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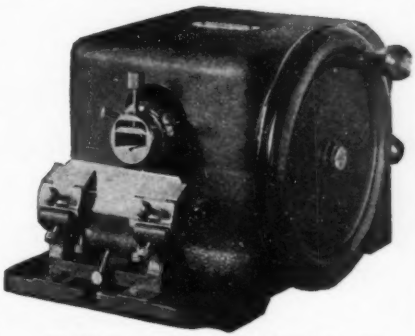

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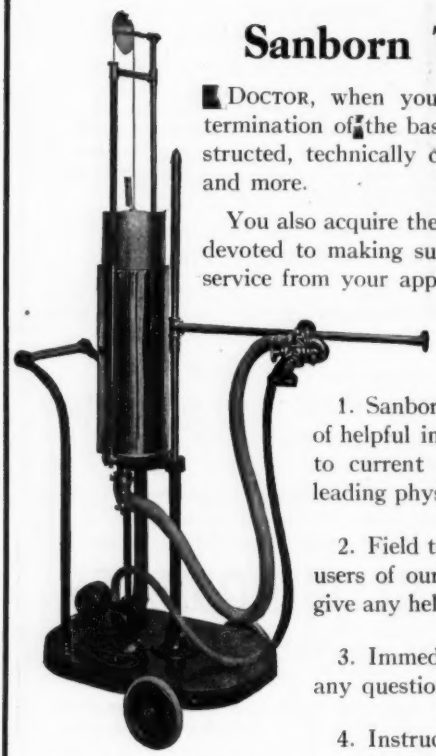

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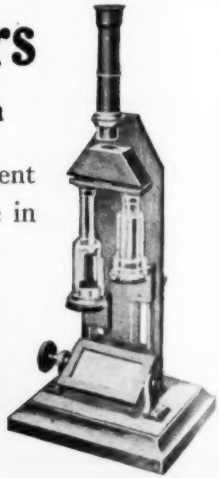

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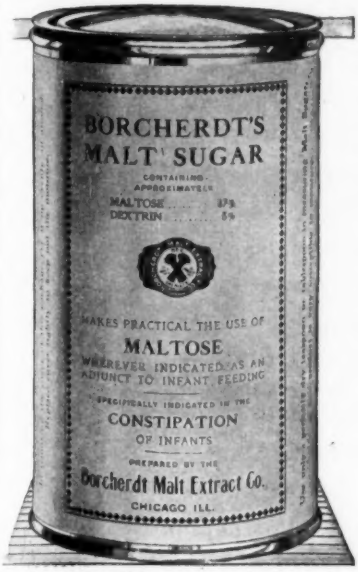

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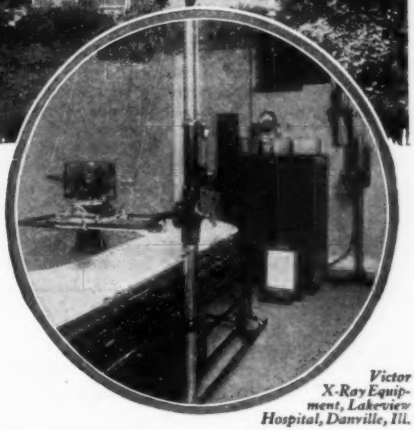

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NOVEMBER, 1921

ORIGINAL ARTICLES.

THE PATHWAYS OF INFECTION IN THE NERVOUS SYSTEM.

A PRESIDENTIAL ADDRESS TO THE NEW YORK NEUROLOGICAL SOCIETY.[1]

By Foster Kennedy, M.D., F.R.S. (Edin.).

Something less than eleven years ago I came to New York to undertake the duties of chief of clinic at the Neurological Institute. I had then a few American friends, whom I had made in London, but none were here; yet the amazing kindness of this country has since made the number of my friends here legion, and the honor you have done in making me your president is an index of the generosity and gentleness of your hearts toward those of different antecedents and training from yourselves.

There is a host of resemblances in the customs of the two great branches of the English-speaking peoples, but one might say with justice that the attitude toward the stranger differs on the two sides of the Atlantic—in Great Britain he is to be viewed socially with suspicion until he proves himself innocent, while in this kindly country he is accepted at something more than his face value until his actions betray him. It is a nice point, therefore, whether my position in this honorable society is to be attributed to my subtlety or to your goodness, nor should I wish for personal reasons to press these researches too closely. Instead I thank you in all gravity

[1] Delivered February 1, 1921.

for the trust you have shown me, which I shall do what in me lies to deserve.

A few weeks ago there was held a meeting of the newborn Association for Research in Nervous and Mental Diseases, an organization fathered by this society, which will be regarded, we trust, in the next couple of decades as a really constructive effort in our branch of medicine. In this concerted attempt to investigate thoroughly a single disease picture, we discovered our strength as clinical observers and as pathological anatomists, and our need of aid from those with knowledge in other fields than our own. From the collected evidence, we gleaned the idea that epidemic encephalitis was an organismal reaction rather than a specific clinical entity; that its picture was drawn and colored probably more by the physiological function of the structure attacked than by the specificity of the virus. We examined carefully the morbid tissues of fatal cases; we explored the battlefields, but made little mention of the roads by which those stricken places were reached by the invading armies. We found that the bulk of individuals with encephalitis had evidence of an injury to the mesencephelon, to the striate bodies and to the red nucleus; we found that, most usually, the first sign of infection other than general malaise was diplopia dependent on a disintegration of function in the oculomotor nuclei, a district at first sight not easily accessible to exogenous poisons. Without speculation on this anomaly of disease incidence, those of us, who consciously deliberated on this phenomenon at all, were content weakly to ascribe to the poison, or group of poisons, responsible for the disease, unknown properties of specific chemiotropism for the nerve structures initially damaged.

This has seemed to me, therefore, an appropriate occasion on which to examine, even without detail, some of our knowledge regarding the routes by which bacteria and toxins, organic and inorganic, can achieve admission to the highways and byways of the central nervous system. In doing so, I cannot hope to tell you any new thing, but rather to refresh your memories of work done in the past and overlain by the accumulations of more recent times. It is well occasionally that we take stock of our possessions; those we have had for long grow dusty and unrecognizable, and we often fail to see how they complement and illumine our baubles acquired but yesterday. The Minotaur was found and slain in the labyrinth only by the aid of Ariadne's guiding threads, and in our searchings we must see to it that some of these be held unbroken.

The bases of our knowledge of the properties of nervous tissue, laid down almost entirely in the lifetime of our senior members, were of necessity anatomical and physiological. The notion of the ancients had to be dispelled—not so many centuries ago—that the purpose of the brain was but to cool the hot and noisome vapors

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arising from the heart! Analysis of centers, tracts and functions have given us a storehouse of knowledge incredibly large indeed, when one considers the short time that has elapsed since groups of men seriously began to apply themselves to neurological problems. When, however, these were beginning to be solved little or nothing was known of infection, bacteriology was still unborn, and to explain morbid processes, men were oriented toward innate degeneration and deficiency of vital forces rather than to the guerrilla warfare, which we now know to be waged unceasingly in our bodies, between our cells and humors on the one hand and an implacable host of microscopic and ultramicroscopic organisms on the other.

The assumption of death of specific tracts and centers before the rest of the organism, of a simple vital lack in a few cells or fibers satisfied us when we were unconscious of the roles capable of being played by insidious infections; so amyotrophic lateral sclerosis, among other ills, was explained by an abacadabra charm called abiotrophy, and the great group of the myopathies was similarly incanted, though we feel ourselves now on the threshold of knowledge of their morbid courses by the portal of the endocrines.

In the presence of your retiring president it might be an impropriety in me to dilate much on this last notion, but I may submit that a consideration of the pathogenesis of the infections of the nervous system may reveal a unity of morbid process in many ailments clinically unlike, a pathological synthesis at least as valuable as the meticulous analyses of symptoms to which we have been accustomed to bend our minds.

The reaction of each of us to a given infection varies (could we but notice the variations) with the different physical personalities which we possess; perhaps—though this is a seven-league step—with the different kinds of endocrine balance in each of us! Our senses require training to detect differences between similar-appearing objects; I remember my difficulty in Russia in distinguishing one acquaintance from another, and on my return, for the first few days the feeling that I knew all the passers-by on a London street because of their general racial and facial resemblance to my friends and relations. So I believe that in the future we shall be able to perceive small individual reactions to toxins from without, reactions which we now look at but do not see. Further, just as one man differs from another in his reaction to infection, so in a single organism there is a host of unknown and little thought of circumstances which determine the incidence and distribution of the lesions—a case of Addison's disease has tuberculosis of the adrenal glands, but one would like to know why he has not a tabes mesenterica or a fibroid phthisis instead.

But such problems at present are merely exasperating, though they will be solved, and some, not improbably, in our day. A

statement of such an example, however, shows our modern wish to be dissatisfied with the mere nomenclature of disease and our desire to dig into the basic study of the conditions of liability and resistance to infection in the various tissues and organs of the body.

The sentry guarding the gate by which infections most commonly reach the central nervous system is the cilia of the mucosa of the airways and especially, perhaps, the mucoid material with which the mucosa is lined. Bayliss has stated that it is mucin which protects the digestive tract from the effects of its own juices, and it is likely that ferment action from dead or living bacteria effects the first rent in the epithelium, giving access therefrom to the lymphatic and blood systems. Benians has demonstrated that Shiga's bacillus can be held alive and harmless in the organism for months if surrounded by mucilage of tragacanth, and this without the production of antibodies in the host against the bacillus. It has been shown that bacteria in carriers are always interned in a mass of mucus, nor have carriers usually developed an active immunity against their potential parasite. In the British training camps and barracks an unduly high carrier rate for the meningococcus invariably preceded the outbreak of an epidemic of cerebrospinal fever, and a task still to be done would be to discover if there be any relationship between susceptibility to infection and nasopharyngeal disease, involving a defect of mucoid secretion—an objective to be gained not alone in cerebrospinal fever but in epidemic encephalitis and poliomyelitis as well.

I have just said that epithelial destruction of mucous membrane is the prelude to invasion of the lymphatic and blood systems by bacteria and their toxins; over the respective roles of these two systems, in conveying noxious material to the nervous system, much recrimination has occurred. As in most controversies there is some truth on both sides, but I believe that an examination of the evidence will in our day dispose of neutrality of thought in the matter. Despite the state of philosophic doubt in the minds of Alford and Schwab, it would appear that the defensive mechanism of the choroid gland in excluding all hematogenous material unsuited to its purpose coupled with the anatomical continuity of the lymph system with the cerebrospinal pons—a continuity accepted by such observers as Halliburton and Starling—make it more than a working hypothesis that, by the perineural and endoneural lymph channels of the cranial and spinal nerves, toxins can reach with unfortunate ease the cerebrospinal axis.

Twenty years ago experimenters were struck by their utter failure to produce characteristic brain and cord lesions by the intravenous injection of bacteria of high virulence; we are now aware of the role played in elective filtration, to use Mestrezat's phrase, by the choroid plexus, whereby large colloid molecules are forbidden access to central nervous tissue—the whole group of

albumenoid toxins are thus cut off from direct invasion of the brain space; I have said *direct* invasion for these large molecules can pass easily through the walls of the capillary vessels, so breaking from the blood to the lymphatic economy. This permeability of the capillary wall is an important factor in the mechanism of many of our infections; Marie, confirmed by Meyer and Ransome, showed that tetanus toxin passed to the lymph vessels from the initial lesion, thence to the blood, thence to the motor end-plates, thence by efferent nerves to the spinal cord—and it has further been shown that if these same nerves be cut an otherwise lethal dose of tetanus can be given without any cord involvement at all; the incubation period in experimental tetanus varies in warm-blooded animals with the length of peripheral nerve tissue to be traversed, a few hours in rats to several days in the horse. When the lower segments of the cord were already the seat of experimental tetanic irritation, it has been always possible to prevent cervical implication by dorsal section, and it is interesting to note, further, that dolorous tetanus, produced by the injection of the posterior roots proximal to the ganglia, was in no instance accompanied by any sign of ventral horn irritation.

However, tetanus intoxication takes place through both the blood and lymph systems, and in experimental intoxication the poison can be demonstrated in the blood even in the earliest stages, but in a state of high dilution; it reaches the subarachnoid spaces of the lumbar enlargement in a much higher concentration through the lymph spaces of the peripheral nerves. One must notice, however, that trismus is one of the earliest signs of the onset of generalized tetanus even when the initial lesion has been in one of the lower extremities. This would seem to be an evidence of a blood-borne toxemia, though the mechanism by which the motor root of the fifth nerve is thus early irritated is by no means clear.

Might I bring to your attention in this connection that in diphtheritic nerve intoxication oculomotor palsy is a constant feature of the disease wherever the infecting focus may be in the body, and we have referred already to the very usual early infection of the third nerve nuclei in epidemic encephalitis. This special susceptibility, to react to general infection on the part of the mesencephalic nucleus of the motor fifth nerve and on the part of the mesencephalic oculomotor nuclei, may not be due simply to an undue delicacy of these structures but may depend on anatomical avenues for invasion as yet not comprehended.

A consideration of the mass of diphtheritic infections occurring in the course of the Palestine campaign has led Walsh away from the idea that this virus is exclusively blood-borne with special affinity for discrete areas of nerve tissue, and toward a notion of the part played by the process named by Orr and Rows lymphogenous toxi-infection of the nervous system. Among the troops operating against the Turks there was an outbreak of so-

called desert sores, which in certain units of the Egyptian expeditionary forces affected 40 per cent of the men. These sores were thought to have some connection with the horse manure laid down on the desert roads, for they ceased to be a military anxiety when the army had attained the fertile plain of the Promised Land. From almost all of these sluggish ulcers Klebs-Loeffler bacilli were recovered in nearly pure culture, and a vast number of cases of peripheral neuritis ensued. The most important observation made by Walsh on this material was that invariably there was an initial local paresis related anatomically to the site of the infective focus—a circumstance in itself disposing of the idea that in such conditions the poison is entirely carried by the blood to the nervous elements; the poliomyelitic virulence of the mesenteric lymph glands of subjects, whose blood is innocuous, is another circumstance of moment in the same connection. At least two of these diphtheritic cases should be quoted here briefly: One, an artillery driver, who suffered from multiple septic sores on the thighs and buttocks and a large ulcer in the perineum also of ten weeks' duration. In the seventh week of his illness he began to experience numbness around the anus and on the buttocks. This sensation of deadness spread to the penis, scrotum, and to the backs of the thighs; a few days later there was loss of control of the bladder and rectum. Not for weeks after the appearance of these conditions did the signs and symptoms of a mild subacute toxic polyneuritis occur, by which time there was also a ready fatigue of visual accommodation. On examination, this man was found to have complete loss to all forms of sensation over the skin areas supplied by the fourth and fifth sacral roots and severe loss of sensibility over the second and third sacral root areas. It was noticed that the segmental symptoms were improving *pari passu*, with an increase in those referable to the terminal nerve twigs.

The second case I ask your leave to quote is that of a medical officer, who infected his right thumb when performing a tracheotomy upon a fatal case of laryngeal diphtheria. In seven weeks the digital wound had healed, but he began to notice numbness and loss of feeling in the affected thumb, signs and symptoms which spread to the radial part of the hand and subsequently were present in the entire hand and forearm. At the same time ataxia and loss of power developed in the right upper extremity. After these disabilities had occurred in the limb he sustained a generalized multiple neuritis, but did not experience accommodation paralysis.

Neither of these patients had any affection of the palate, in which circumstance they were identical with the other cases of paralysis following extrafaucial diphtheria.

Perhaps I might be allowed to correlate with this material, those cases described by myself as acute infective neuronitis. These occurred as a minor epidemic among soldiers in the field and were characterized by fever, peripheral neuritis and ascending signs of

involvement of the spinal roots and ganglia. In some of them the posterior roots suffered vastly more than the peripheral nerves, so that root zones of grossly altered sensibility were easily demonstrated. A constant feature of these cases was peripheral paralysis of the face and the lower muscles of deglutition. The pathological picture produced was extraordinarily akin to those obtained experimentally by Orr and Rows in their work on lymphogenous infections and the gross involvement of the spinal ganglia in my cases gives point to the suggestion that these structures may act as blocks to the centripetal transportation of lymphogenous poisons.

Severe damage to the cells of the posterior ganglia was a feature also of a series of ascending neuritides of the cauda equina, which I described with Charles Elsberg in 1913, and the arguments for the lymphogenous nature of the virus in tabes through the changes in the dorsal root entry zone are sufficiently familiar to warrant no more than a passing mention in an address already growing overlong. We should notice, however, the interesting fact that degeneration of exogenous fibers invariably begins at the point where the neurilemma leaves off and that, in fatal cases of diphtheritic poisoning, where the palate has been entirely disabled, the vagal nuclei have been found destroyed without any evidence of injury to the vagi themselves. Whether the influence of the neurilemma on the axis-cylinder be protective or nutritive, whether it be vital or mechanical or whether its role is an integral part of neural conduction is one of the major problems of neurology today. Before turning from these surface speculations on some of the avenues of infection of the central axis, we should refer suggestively to Collins and Armour's autopsied case of acute bulbar palsy in a child with mumps; and especially to a series of cases described by Wilfred Harris of chronic bulbar palsy immediately following diphtheria, clinically resembling myasthenia gravis, but differing from that condition by the absence of ptosis, dyspnea or variability of disease picture, and by the presence of muscular atrophy and the reaction of degeneration. Dr. Dana has described amyotrophic lateral sclerosis directly produced by lues; a group of patients with chronic lead poisoning suffering from the same disease has come under my own observation, and Stanley Barnes has recorded a number of patients with a chronic toxic affection of the lower motor neurone, having a tendency to slow improvement following acute specific fevers.

It is fair to suppose, therefore, that further investigation of the routes, by which infections attain the brain and cord, may reveal much regarding the pathogenesis of some nervous ailments. We can hope, however, to illuminate only a few problems by any one method. Thus an attempt, and one somehow appealing, has been made recently to show that the location of the lesion in the combined spinal sclerosis of anemia and marasmus depends ultimately on a depreciated adrenal activity operating on the spinal pial ves-

sels through the thoracicolumbar sympathetic chain. One may add that some such synthetic imagining is required to account for the so-frequent incidence of spinal tuberculosis in the fifth or sixth dorsal vertebræ. The clinical phenomena of acute multiple sclerosis suggest a perivascular outpouring of fluid into the nervous elements, to study which adequately requires more than a notion of the conditions governing osmotic pressures in living organisms, and possibly also of colloidal chemistry and the specific action of calcium ions in producing abnormal permeability of capillary vessels. Indeed, the whole question of radio-active salts on cell function might well have to be determined before a satisfactory explanation of such a well-recognized clinical process as I have just mentioned can be forthcoming.

The development of all branches of medicine has led to diversion of talent into a variety of areas as separated from each other as though each observer were in a kite balloon by himself—nor have we evolved any adequate headquarters where reports from each can be received and correlated. The modern student receives instruction in animal physiology from physiologists who never enter a ward, in chemistry from chemists often without interest in either physics or biology; structure and function in his mind are in different water-tight compartments so that in the beginning of his clinical years he is in travail to apply his knowledge to the problems before him, and must needs explain a hemianopia by a possible lesion of the bundle of Vicq d'Azyr. The same segregation of different branches of knowledge is continued into our adult professional lives. As a society for the advancement of learning we must try to arouse interest in our problems among physiologists and biological chemists, among pathologists and anatomists; we should seek to include them in our body. Their science would be more humane, our medicine more scientific. I should go even further than this, for I can see no disability but a great gain, through a new orientation, if sometimes we were to choose to lead us, a man, not of our specialty, but one of erudition in some cognate sphere, with sympathy for our state of darkness. No one can play equally sweetly on all the instruments of an orchestra and the conductor should be changed with the kind of music to be played.

In all civilizations known to us there has been a fairly regular sequence in the flowering of thought: First, there develops carving and painting and building as expressions of the human spirit, then comes literature and, last of all, science strides forward. For us, this last cycle is but beginning, and there will be time enough before the great changes are rung in the world to lay down principles, the knowledge of which may with fortune be stored up for the peoples who will come after ours. Let there be but coöperation among all kinds of us and then, "Turn you to any cause of policy, The Gordian knot of it you will unloose, Familiar as your garter."

THE EFFECT OF TREATMENT FOR SYPHILIS ON SEVERE ANEMIAS

H. O. Foucar, A.B., M.D.,

FELLOW OF THE MAYO FOUNDATION, GRADUATE SCHOOL, UNIVERSITY OF MINNESOTA.

AND

John H. Stokes, A.B., M.D.,

CHIEF OF THE SECTION OF DERMATOLOGY AND SYPHILOLOGY, MAYO CLINIC, AND ASSOCIATE PROFESSOR OF DERMATOLOGY, THE MAYO FOUNDATION.

Fournier in reviewing the anemias of syphilis states that the disease causes a diminution in the percentage of hemoglobin, a decrease in the number of erythrocytes and an increase in the number of leukocytes. He recognizes five types of anemia in association with the disease: (1) the simple secondary anemia (by far the most common), (2) chlorotic anemia, (3) chlorotic anemia with leukocytosis, (4) leukemia and (5) (infinitely rare) syphilis imitating the picture of pernicious anemia.

Fournier refers to the difficulty in some cases of deciding whether syphilis is the direct cause of these modifications or whether they are the result of associated symptoms (the febrile state, symptoms of dyspepsia, nervous troubles, superimposed infections or the influence of misguided therapy). He quotes the old saying that "mercury is the iron of syphilitic anemia." However, after having corrected the syphilitic changes, mercury becomes, in turn, an alterant of the blood. For a time it does good, later it becomes harmful. Mercury cannot be given over a prolonged period without damage. Fournier instituted, therefore, the "method of successive or intermittent treatments."

Since Fournier's time little has been added to our knowledge of the mercurial therapy of syphilitic anemias. The advent of arsphenamin has brought new possibilities, which, although extensively discussed in the abstract, have been reinforced by only a small body of clinical material. This paucity of clinical discussion may be ascribable to the comparative rarity of pernicious anemia in combination with syphilis. The total number of cases with or without syphilis treated with arsphenamin which have been collected from the literature is thirty-six. To this are now added the twenty-five cases of severe anemia which form the basis of the present study. Primary emphasis is laid on the effect of arsphenamin therapy, since the cases were originally approached from this angle.

REVIEW OF LITERATURE

Arsenic was first used in treating pernicious anemia with gratifying results in 1875 by Bramwell. In 1911 he began using arsphen-

amin, one to four injections of 0.3 gm. each intramuscularly, because he desired to secure a gradual and prolonged action of the arsenic constituent of the drug. In 1913 he reported his experience with twelve patients, of whom two showed no change, three showed slight improvement and seven were greatly benefited, although one had a relapse later.

Leede, in 1911, treated five patients with pernicious anemia *in extremis*. Four of them died in from thirty-six hours to fourteen days, and Leede therefore concludes that arsphenamin is directly contraindicated. He also reported a case that gave the impression of pernicious anemia, atypical however. A diagnosis of anemia with a syphilitic basis was made. After one injection the hemoglobin rose from 15 per cent to 60 per cent and the erythrocytes from 900,000 to 4,000,000 in two months. The hemoglobin fell to 50 per cent and a second injection was given; the hemoglobin then rose to 70 per cent in eight days. Leede pointed out the need for splitting up pernicious anemia into further groups (due to *Bothriocephalus latus, Ankylostoma, and so forth*).

Steyrer, in 1912, after treating a patient for some time with Fowler's solution and seeing no improvement, gave several injections of arsphenamin. The hemoglobin rose from 20 per cent to 70 per cent, and the erythrocytes from 700,000 to 4,500,000, with the disappearance of megaloblasts and poikilocytosis.

Friedlander, in 1912, reported a case in which the patient had received large quantities of arsenic and iron. The erythrocytes numbered only 887,000 with 20 per cent hemoglobin, giving an index of 1.1. After two injections of 0.3 gm. arsphenamin and injections of 1 gr. of cacodylate of iron on alternate days for twenty-seven days the erythrocytes rose to 3,200,000, the hemoglobin to 52 per cent, with an index of 0.7, the picture of only a mild anemia.

Hobhouse, in 1912, added one case to the list. His patient had been anemic for more than a year and had improved under large doses of arsenic. In October there was no sign of pernicious anemia, but in May the count showed 800,000 erythrocytes and 18 per cent hemoglobin, with an index of 1. Two intramuscular injections of 0.3 gm. of arsphenamin were given and in October the erythrocytes numbered 4,704,000, hemoglobin 110 per cent, with an index of 1.05.

Boggs, in 1913, reported eleven cases. Three of the patients died. One was moribund at the time of injection and one died eleven days after the administration of 0.2 gm. of arsphenamin. The reaction was not marked and the blood count did not drop more than 200,000 erythrocytes. The third patient improved, the count rose from 1,100,000 to 3,400,000 in twenty days, eventually reaching 4,800,000, with 85 per cent hemoglobin; the patient, however, died later. The picture was never free from the qualitative changes of pernicious anemia. Five patients improved with an initial drop of never more than 200,000 erythrocytes. One received 0.3 gm. intravenously

every four weeks. In sixteen weeks the erythrocytes rose from 500,000 to 5,000,000 and the hemoglobin from 23 per cent to 90 per cent. Two other patients had an average rise of 2,000,000 erythrocytes. Although all precautions were observed a sharp febrile reaction after each injection lasted from six to twelve hours, in contrast to the very mild or absent reactions in syphilitics. Boggs concludes that the drug may be given without serious risk, and the results justify its use in pernicious anemia.

Maynard, in 1913, noted a slight increase in erythrocytes after a first injection of arsphenamin; after a second, however, there was a decrease, and he did not use it further.

Weicksel (1913) thinks that syphilitic pernicious anemia is not the result of syphilis, but that under certain predisposing conditions syphilis sometimes leads to this disease. According to him syphilitic anemia is seen in general in latent syphilis. He reports one case, that of a man, aged fifty-two years, with a moderately positive Wassermann reaction and a typical pernicious anemia. The patient was given two injections of arsphenamin and reactions followed which confined him to bed. The erythrocytes subsequently rose from 1,680,000 to 3,700,000 and the hemoglobin from 45 per cent to 85 per cent; the index fell from 1.34 to 1.08. This, however, brings up the question of whether arsphenamin produced the improvement or the collateral treatment for the pneumonia which developed. In the syphilitic pernicious anemia the situation is more favorable, because there is a remedy against the syphilis. Weicksel, in a second article (1913), reported the death of the patient and the pathologic findings of pernicious anemia. Either the old syphilis had no connection with the anemia and the condition was a so-called cryptogenetic form of pernicious anemia or the anemia was the result of a former syphilis for which insufficient arsphenamin had been given to remove the cause. Weicksel inclines to the latter view and advises the use of arsphenamin in further cases.

Lämpe, in 1916, treated three patients suffering from pernicious anemia by the intravenous injections of small doses of arsphenamin, 0.05 gm. to 0.15 gm.; the hemoglobin rose 40 or 50 per cent and the erythrocytes were increased 2,500,000. One of the patients had a remission and died. Lämpe states that he has never seen similar favorable results in cases of pernicious anemia that have been treated in other ways.

Lowrey, in 1917, reported a case in which pernicious anemia developed some time after treatment with arsphenamin, and he decided that there is probably no causal relation.

It will be noted that all the foregoing cases had been diagnosed pernicious anemia and only in a few instances was there any mention of syphilis. Other than these reports we have been unable to find any series which dealt primarily with the effect of arsphenamin on anemia associated definitely with syphilis. Hirschfeld (1918) makes

the general statement, however, that in a few cases syphilis in its tertiary stage may present the symptom-complex of pernicious anemia. Treatment of syphilis, preferably with arsphenamin, "cures the disease, without a remission." Each patient with a positive Wassermann reaction, however, should not be regarded as syphilitic. Old syphilis is more often an associate than a cause of pernicious anemia. Hirschfeld has repeatedly seen cases of this type in which treatment was given for syphilis without success. The question concerning the syphilitic etiology is determined only by the success of specific therapy. It is always possible that the anemia has progressed so far that in spite of the control of the syphilis a normal regeneration of blood can no longer take place. This must be considered, particularly if during treatment the Wassermann reaction becomes negative and the blood findings are not improved.

EFFECT OF ARSPHENAMIN ON THE BLOOD PICTURE

Numerous investigators have studied the blood picture of syphilitics under treatment with arsphenamin. In most cases the examinations were routine and made without particular reference to anemia. Lévy-Bing, Duroeux and Dogny, however, confined their reports to cases presenting definite anemia.

Von Besaiss, in 1911, noted, besides a hyperleukocytosis, marked increase in erythrocytes under arsphenamin treatment. In one case of tertiary syphilis the erythrocytes were unaltered, and in this case the preparation failed therapeutically.

Magat, in 1910, studied the blood and urine in three cases of recurrent fever, fifteen of syphilis and several of malaria treated by Georgyewsky. He speaks of the increase in erythrocytes and in hemoglobin with a decrease in leukocytes the first day after injection of arsphenamin.

Evdokimow, in 1911, observed a more or less distinct improvement in the blood picture under arsphenamin. The fluctuation in hemoglobin was transitory and rarely exceeded 8 per cent. Usually there was a slight increase in erythrocytes, a more or less marked leukocytosis with increase in eosinophils and a more frequent increase in neutrophils.

Baugher and Vaughan, in 1911, treated eighteen patients with syphilis, the erythrocytes and hemoglobin showing no constant change. There was an initial drop in leukocytes in the first few hours after the injection, a rapid increase during the first twenty-four hours, reaching a maximum in from two to four days, becoming normal or slightly above normal in from six to ten days.

Dorn, in 1912, stated that following intravenous injection of arsphenamin there is a hemolysis of short duration, with a decrease in hemoglobin, sometimes as great as 20 per cent, and a drop in

erythrocytes with the presence of urobilinogen and urobilin in the urine. The blood count returns to its former level or even a little higher in twenty-four hours.

Thevenot and Brissaud (1912) believe that arsphenamin causes an excitation of hematopoiesis. The erythrocytes show at first a diminution of sometimes 1,000,000. In fifteen days there is an increase of from 500,000 to 2,400,000.

Schwaer, in 1912, treated twenty-four syphilitic patients with positive Wassermann reactions whose blood pictures varied but little from normal. The hemoglobin showed but little change, from 5 per cent to 10 per cent either way, usually down, irrespective of the dose, 0.2 gm. to 0.6 gm. There was no definite alteration in the erythrocytes. Schwaer used small doses, 0.05 gm., in anemias of different etiology with practically no effect, and concludes that as then employed arsphenamin did not seem to have a place in the treatment of diseases of the blood in general.

MacKee, in 1912, investigated twenty-one cases before and after treatment and noted a very definite relation between the systemic reaction and the fall in erythrocytes, when, as he believed, the reactions were produced by the use of stale distilled water. In his opinion arsphenamin itself plays no part in reducing the count, for if there was no systemic reaction there was no substantial reduction in the number of erythrocytes and no reaction occurred with proper technic.

Lévy-Bing, Duroeux and Dogny used from one to three injections of 0.3 gm. of arsphenamin in neutral suspension in ten cases of secondary syphilis. All the patients were moderately anemic, 3,200,000 to 3,800,000 erythrocytes. No appreciable change in hemoglobin was noted. There was a varying diminution in erythrocytes, 300,000 to 500,000, returning to the former count. There was no amelioration of the preëxisting anemia.

Wawiorowski, in 1912, using subcutaneous and intravenous injections of arsphenamin, found only a slight effect on hemoglobin and erythrocytes.

Heden (1913) gave from three to eight intravenous injections (average six of 0.4 gm. arsphenamin or its equivalent) in fifteen cases. After the first treatment there was a slight decrease in hemoglobin, 10 per cent at most, less after the second and third treatments and none later. The same held true for erythrocytes.

Yakimoff, in 1911, from experimental work on rats, normal or infected with *Spirochæta duttoni* and *Trypanosoma gambiense*, concludes that arsenobenzol causes first an inhibition of the hematopoietic organs and later an excitation. The reaction in monkeys is similar.

Kolmer and Yagles' work (1920) on the hemolytic activity of solutions of arsphenamin and neoarphenamin shows that hemolytic activity depends on (1) the direct action of arsphenamin, (2) the

use of nonisotonic solvents, and (3) the use of sodium hydroxide, especially in excess of that needed to produce the disodium arsphenamin salt.

It appears from the foregoing *resume* that of nine clinical investigators six report favorable results from arsphenamin in anemia, one is opposed to the treatment and two are undecided or give qualified opinions. Among investigators of the laboratory aspects of the problem of the influence of arsphenamin on the blood, five are in favor of the drug as a means of producing a rise in hemoglobin and erythrocytes and seven are against or give qualified opinions. In general it appears that there is a transient destruction of erythrocytes followed by a rise whose degree and permanence vary in different opinions.

CASES OBSERVED IN THE MAYO CLINIC

During the last four years approximately 4800 patients with syphilis have been treated in the Section on Dermatology and Syphilology of the Mayo Clinic. These are largely patients with late or latent syphilis who have come to the Clinic on account of nervous, cardiac or gastric symptoms, although there is a fair percentage with primary or secondary manifestations. In the examination of the records of these patients it was found that in the majority the hemoglobin was 70 per cent or more. It seemed advisable to study only those with 55 per cent or less. Only twenty-five patients were available for such a study. These were all patients in whom the diagnosis of syphilis was either unquestionable or in whom it was sufficiently plausible to warrant a therapeutic test. Patients with proved or suspected syphilis were chosen because if arsphenamin will help any type of anemia it should help the type with a possible syphilitic basis.

Three types of cases are possible in this group of anemias:

Type 1, true pernicious anemia, giving a nonspecific positive Wassermann reaction.

Type 2, true pernicious anemia in association with syphilis.

Type 3, severe anemia due directly or indirectly to syphilis.

Cases were regarded as proved syphilitic, in which there was at least a definite history, a positive Wassermann test and remnants of an old infection or signs at the time of examination of involvement in any system. Cases in which there was either no history or only a doubtful history of a primary lesion, with no clinical evidence of syphilis, or in which only one positive Wassermann reaction had been obtained were regarded as doubtful. Cases were classified as a pernicious type of anemia in which the blood picture showed a decrease in erythrocytes out of proportion to the fall in hemoglobin with the presence of anisocytosis, poikilocytosis, nucleated erythrocytes and clinically by weakness, dyspnea, sore-tongue, gastro-

intestinal disturbances, pigmentary changes (lemon tint) and sometimes nervous manifestations. Obviously little may be expected in the first two groups from treatment for syphilis, *per se*, except insofar as the drugs used primarily against syphilis may also have a direct beneficial effect on the anemia, either by stimulating hematopoiesis or by preventing blood destruction.

METHODS AND TREATMENT

Schamberg's preparation of arsphenamin, obtained from the Dermatological Research Laboratories, Philadelphia, was used in most cases in increasing doses, 0.3 gm. to 0.5 gm., at weekly intervals. In a few cases Lowey's solution of arsphenamin was used. Novarsenobenzol was substituted when the patient's condition indicated. Occasionally the dosage was reduced. After the patient had been given a course of six injections, during which time his tolerance for mercury was ascertained, he was sent home for from one to three months with or without mercurial treatment in the form of 4 gm. 33 per cent inunctions, or *hydrargyrum cum creta*. Second and even third courses were given to some of these patients.

Transfusions were given to certain patients prior to, concomitant with, or following specific therapy. They were given by the citrate method, the donor and recipient usually belonging to the same group, although in emergency a Group IV donor was used irrespective of the recipient's group. The usual quantity given was 500 cc.

The Dare hemoglobinometer was used throughout. The recent work of Senty, in which he showed that readings above 70 per cent were subject to error, needs mention. Below this, however, the estimations are accurate. In this series, then, the readings may be considered correct apart from the variations due to personal equation. We have arbitrarily taken increases or decreases of 5 per cent as legitimate error and have paid attention only to greater changes.

The Wassermann technic as carried out at the Clinic under the direction of Dr. A. H. Sanford is a slight modification of the original Noguchi system. In the preparation of the amboceptor, dogs instead of rabbits have been used. Human corpuscles have been sensitized by adding a definite amount of amboceptor to the washed corpuscles and placing the mixture overnight in the ice-box. The sensitized cells are then titrated against various amounts of 40 per cent diluted guinea-pig serum. The standard antigen for routine work is an acetone-insoluble fraction of heart extract.

We have been more interested in the effect of arsphenamin on the course of anemia from day to day and from week to week than in the immediate effect on the blood picture. No attempt has been made to learn whether there was an initial drop in the first few minutes or hours with a subsequent rise to the original count or

above. This has been the object of study by several investigators, and the results have been uniform.

Tables 1, 2, and 3 classify our material from various standpoints.

TABLE I.—EVIDENCE OF THE PRESENCE OF SYPHILIS IN RELATION TO THE BLOOD PICTURE

Evidence of syphilis.	Pernicious anemia.	Secondary anemia.	Undetermined,[1] (hemoglobin only.)	Total.
Indisputable	5	5	1	11
Wassermann test and history	1	1		2
Wassermann test only	6	3	1	10
History only	1	..	..	1
No history. Wassermann test negative	..	1	..	1
	13	10	2	25

It will be seen that about half the cases in this series presented the picture of pernicious anemia. A positive Wassermann reaction as the only evidence of syphilis was encountered twice as frequently in pernicous anemia as in secondary anemia, perhaps supporting the theory that this disease may of itself yield a positive Wassermann reaction in the absence of syphilis (Sanford).

TABLE II.—CLINICAL DIAGNOSIS

Pernicious anemia:	
Definite	6
Probable	4
Atypical	1
Associated with gastric syphilis	1
Associated with hepatitis and cutaneous tertiary syphilis	1
	13
Secondary anemia:	
Anemia prominent	3
Associated with hereditary syphilis	1
Associated with aortitis	1
Associated with gastric syphilis	1
Associated with syphilitic splenomegaly and enlarged liver	1
Associated with chronic arthritis	1
Associated with gastric syphilis and osteitis	1
Associated with periostitis (syphilis of the ribs?) and empyema	1
	10
Undetermined (hemoglobin estimation only) (clinically secondary in type):	
Tabes dorsalis	1
Hypertension	1
	2

In cases presenting the picture of pernicious anemia the anemia was the outstanding feature and only infrequently were other conditions suggesting syphilis present. Secondary anemia, however,

[1] Clinically secondary in type.

was more commonly associated with some syphilitic involvement of other systems.

TABLE III.—THE EFFECT OF TREATMENT FOR SYPHILIS ON SEVERE ANEMIAS

	Pernicious anemia.	Secondary anemia.	Total.
Patients received mercury	9	9	18
Patients with proved syphilis	3	6	9
Patients sent home on mercury treatment	7	2	9
Patients with proved syphilis	2	1	3
Patients sent home on mercury treatment, hemoglobin fell from 12 per cent to 35 per cent	4		4
Patients with proved syphilis	2		2
Patients received arsphenamin	13	12[2]	25
Patients with proved syphilis	5	6	11
Patients without change under arsphenamin	3	6	9
Patients with proved syphilis	1	5	6
Patients improved under arsphenamin	5	5[2]	10
Patients with proved syphilis	2	1	3
Patients became worse under arsphenamin	5	1	6
Patients with proved syphilis	2		2

Mercury was given with arsphenamin and therefore it was often difficult to estimate its effect, which is best judged by watching the results when it is given to patients during their rest period between courses of intravenous injections. In four of nine patients a reduction in hemoglobin of from 12 to 35 per cent and a decrease in erythrocytes of from 500,000 to 2,000,000 were noted under inunctions. In all of these patients showing a decrease the blood picture had approached that of pernicious anemia from the start. They had previously improved from 18 per cent to 30 per cent under arsphenamin therapy. The relapses may, of course, have been purely a coincidence. While long experience may have shown mercury to be "the iron of syphilitic anemia," it must evidently be used with caution in the more severe grades, particularly when the picture approximates that of primary pernicious anemia. In two of the patients who reacted unfavorably to mercury, arsphenamin barely maintained the blood picture, while transfusions maintained it at a slightly higher level. One patient's hemoglobin continued to fall from 56 per cent to 36 per cent under three arsphenamin injections, but one month after a single transfusion the hemoglobin had risen to 67 per cent, the erythrocytes to 4,280,000, giving an index of 0.7, compared with hemoglobin 36 per cent, erythrocytes 1,530,000, and an index of 1.1. The fourth patient was apparently improving

[2] Including two indeterminate cases (hemoglobin only) clinically secondary, one with definite syphilis.

under arsphenamin therapy when a reaction, following an intravenous injection of the drug, resulted in a rapid decline, and only by repeated transfusions was the hemoglobin raised from 33 per cent to 46 per cent and the erythrocytes from 1,750,000 to 2,510,000. It is apparent at least that the patients reacting unfavorably to mercury showed evidence of a tendency to an unfavorable course.

With regard to the effect of arsphenamin in our series the drug has been given with reasonable safety even in patients whose hemoglobin is 20 per cent, although it seems a better policy to increase this to 30 per cent by transfusions, if possible, before starting specific therapy. Every precaution must be taken to prevent reactions, for accidents which may be only disagreeable in otherwise healthy persons assume dangerous proportions in persons whose condition is already grave.

In six cases a drop in hemoglobin of from 10 per cent to 20 per cent and a decrease of about 500,000 erythrocytes occurred during arsphenamin therapy. To these may be added one case in which an increase had previously been shown following intravenous therapy. In two of these unfavorably affected cases transfusions were of no value. In another the blood count continued to drop for a time even with transfusions, but ultimately, after seven transfusions, the picture improved. The hemoglobin in this case rose from 18 per cent to 48 per cent and the erythrocytes from 1,470,000 to 3,150,000. Despite this improvement the patient died shortly after reaching home. An initial drop in hemoglobin from 70 per cent to 50 per cent with a decrease in the number of erythrocytes from 4,600,000 to 4,000,000 was observed in the fourth case following two injections of arsphenamin. Throughout three subsequent courses in this case the erythrocytes fluctuated between 3,000,000 and 4,000,000 and the hemoglobin between 50 per cent and 60 per cent. In the fifth and sixth cases there was a 5 per cent increase in hemoglobin but a decrease of 500,000 erythrocytes. One of these patients died shortly after transfusion.

In nine cases no definite effect from arsphenamin was noted. Two of the patients received only three injections, a toxic erythema in one rendering it necessary to discontinue the arsenic preparation. The other presented the blood picture of such an advanced pernicious anemia that a transfusion was given but without improvement. He returned home and a letter indicated that his condition was unchanged. Seven patients received from four to fourteen injections without definite effect. Two of these had pernicious anemia with a questionable syphilis and five had secondary anemia; all but one of the latter were proved to be syphilitics.

In ten patients an improved blood picture (an increase of from 8 per cent to 35 per cent in hemoglobin and from 200,000 to 2,000,000

in erythrocytes) followed arsphenamin treatment. Five of them had pernicious anemia. In only three of the ten who improved was the evidence of syphilis indisputable. We are surprised in comparing this group with the foregoing to find the relatively high proportion of patients with pernicious anemia and the relatively small proportion with proved syphilis.

Transfusions were resorted to at some period of the treatment of sixteen patients, either to reinforce those who had made only moderate improvement or as treatment for those who had not responded. If patients did not improve under arsphenamin treatment only it was often combined with transfusion, and later transfusions were given alone. In patients whose initial hemoglobin was 25 per cent or under transfusions were used to bring the hemoglobin above 30 per cent. The estimation of the relative value of arsphenamin and transfusions is more difficult in cases in which the transfusions had been resorted to during the arsphenamin course. For example, one patient during the second course received four injections of arsphenamin and three of novarsenobenzol. Transfusions were given before the first and fourth injections. The hemoglobin at the beginning was 30 per cent and at the end 49 per cent, with a reading of 64 per cent following the second transfusion. Arsphenamin had no appreciable effect during the first and third courses. We therefore would feel justified in this case in concluding that the rise was merely due to the temporary beneficial effect of the transfusions rather than that the subsequent arsphenamin injections had counteracted the good effect of the transfusions.

In four instances transfusions gave more gratifying results than did arsphenamin. One of these patients had continued to improve under arsphenamin, the hemoglobin increasing from 40 per cent to 70 per cent. He relapsed under mercury and the third course of arsphenamin sufficed only to hold the hemoglobin at 40 per cent. By repeated transfusions the hemoglobin was maintained between 45 per cent and 50 per cent. In a similar case the hemoglobin dropped from 70 per cent to 56 per cent under mercury and continued to drop from 56 per cent to 36 per cent under arsphenamin. One month after a single transfusion the hemoglobin was 67 per cent. Another patient's hemoglobin improved under specific treatment from 35 per cent to 45 per cent. After receiving a transfusion the patient was sent home. In two months his hemoglobin estimation read 75 per cent, and this was maintained during the next course of arsphenamin. The fourth patient received one course of arsphenamin with slight improvement. Transfusions were combined with arsphenamin during the second course. After the second injection of the third course he had a violent reaction with a rapid fall in hemoglobin. Repeated transfusions raised the hemoglobin from 33 per cent to 46 per cent and the erythrocytes from 1,750,000 to 2,510,000.

In three other cases transfusions improved the blood picture, but the patients died. Transfusion had no effect in four instances and only a temporary beneficial effect in two. In another case following a relapse transfusions were successful in maintaining the count at a higher level, but not so high as it had been previously. In two cases transfusions were used with success before beginning specific therapy.

If, as Hirschfeld says, the proof that a pernicious type of anemia is due to syphilis depends on cure without remissions by means of treatment of the syphilis, no cases of syphilitic pernicious anemia have been recognized in the Mayo Clinic since the organization of the Section of Dermatology and Syphilology. The nearest approach to such a case is that of a man, aged thirty-eight years, with a history of infection and with leukoplakia in the mouth. His spinal fluid and his blood Wassermann test were negative, even with a provocative test. His symptoms and findings, interpretated by several competent observers, were those of a typical primary anemia. His hemoglobin was 55 per cent, the erythrocytes numbered 2,560,000, with a color index of 1. After three transfusions the hemoglobin estimation was 70 per cent with 4,000,000 erythrocytes and an index of 0.8. After two courses of intravenous therapy the patient had 4,750,000 erythrocytes and 85 per cent hemoglobin, and following the third course the erythrocytes increased to 5,040,000. He is the picture of health, has gained 50 pounds and has been well for two and one-half years. Whether his improvement was due to transfusion or to the arsphenamin injections, and whether he is merely having a long remission, cannot be stated. Stockton (1919) recently reported a case of pernicious anemia in which the patient had a remission after twelve years of apparently good health

SUMMARY AND CONCLUSIONS

1. Severe anemia, either primary or secondary, associated with late or latent syphilis, is apparently rare, twenty-five cases appearing in approximately 4800 records in the Section on Dermatology and Syphilology in the Mayo Clinic.

2. Pernicious anemia may be seen in association with syphilis, but no case exhibiting an incontestable etiologic connection has appeared in our records.

3. One patient with the clinical picture of pernicious anemia and a doubtful syphilitic infection has been apparently well two years as a result of treatment.

4. Pernicious anemia in the apparent absence of syphilis may yield a positive serum Wassermann reaction.

5. Mercury by inunction, used alone, produced an unfavorable reaction in four of nine patients with anemias who had pre-

viously improved under arsphenamin, but all had primary anemia and subsequently showed evidences of a relapsing unfavorable course.

6. We believe, therefore, that in syphilis with anemia mercury should be used with caution, especially if the picture suggests the primary type.

7. Five of thirteen patients with primary anemia improved under arsphenamin. Of these two who improved and three who did not had demonstrable syphilis.

8. Five of thirteen patients with primary anemia became worse under arsphenamin; of these two had syphilis.

9. Five of twelve patients with secondary anemia improved under arsphenamin treatment. Of these only one who improved and five who did not had demonstrable syphilis.

10. Only one of twelve patients with secondary anemia became worse under arsphenamin.

11. In our experience, then, arsphenamin has been much more effective in secondary anemia than in primary anemia, but curiously disappointing in secondary anemia with associated manifestations of syphilis.

12. Twelve of sixteen patients improved under transfusion, four of them after arsphenamin had failed. Two of these patients showed only temporary improvement and three others died notwithstanding the improved blood picture. The effect of transfusion could only be judged with difficulty because of the conditions under which it was employed.

13. In four of sixteen cases transfusion was without effect.

14. Transfusion should be a preliminary to arsphenamin when the hemoglobin is below 20 per cent.

15. Reactions to arsphenamin injections must be carefully avoided since they may produce an alarming drop in hemoglobin.

16. No satisfactory rule for determining which case would improve on treatment for syphilis and which case would not could be arrived at. In general half the cases may be expected to improve.

17. The degree of improvement is not necessarily proportional to the demonstrability of syphilis. The pernicious anemia associated with undoubted syphilis which we have seen has run the ultimate course of pernicious anemia regardless of treatment for syphilis.

18. Hemoglobin estimations alone are not sufficient to indicate the progress of the patient. The hemoglobin may rise and the number of erythrocytes fall at the same time.

19. Arsphenamin treatment is safe if carefully used in anemia and should be employed in patients with undoubted evidence of the disease, and, as a therapeutic test, when reasonable suspicion of its presence exists.

20. Transfusion must remain the ultimate resort in primary

cases, and in those cases associated with syphilis in which arsphenamin has failed, even in the presence of syphilis, the best effect will be secured by both together.[3]

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The case is one of definite syphilis with hepatic cirrhosis and splenomegaly. Weekly tappings were necessary. The blood picture was that of a moderate anemia, with hemoglobin 68 and erythrocytes 3,980,000. After a six weeks' course of mercury inunctions with potassium iodide by mouth, the patient improved greatly and did not require tapping throughout this period. His hemoglobin, however, dropped to 50 per cent and his erythrocytes to 2,880,000. The improvement in his general condition continued through three months' treatment with *hydrargyrum cum creta* and with potassium iodide. A course of arsphenamin, 0.2 to 0.4 gm., was given, at the end of which time the hemoglobin had risen to 60 per cent and the erythrocytes to 4,560,000. Splenectomy was then performed. The patient died early the next morning.

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LEUKEMIA IN CHILDREN, WITH SPECIAL REFERENCE TO LESIONS IN THE NERVOUS SYSTEM.

By Murray H. Bass, M.D.,

ADJUNCT ATTENDING PEDIATRIST TO THE MOUNT SINAI HOSPITAL AND THE HOME FOR HEBREW INFANTS, NEW YORK.

(From the Pediatric Service of Mount Sinai Hospital.)

The recent occurrence of two rather unusual cases of leukemia in children admitted to the pediatric service of the Mount Sinai Hospital has prompted me to go over the hospital records of the past ten years and to collect therefrom the cases of leukemia admitted during that time. In tabulating these cases, twenty-three in number, several interesting points are brought out and seemed to me worth while recording. It is distinctly not my purpose to review all the symptoms and signs of leukemia as this disease occurs in children, as this has been ably done by others, especially by Benjamin and Sluka in their monograph *Die Leukæmie im Kindesalter*, 1907, and by A. Strauch in an article published in the *American Journal of the Diseases of Children* in 1913, where a good bibliography may be found. In the review of the cases in the present paper I shall therefore not make any attempt at completeness in describing leukemia clinically, but will stress especially the following points: (1) The type of disease as it attacks children; (2) the common physical findings; (3) the diagnosis of the disease; (4) the symptoms referable to the nervous system.

As our cases well show, leukemia in children is essentially an acute disease. The longest duration of any of our cases was one year (Case 22). Benjamin and Sluka refer to a chronic case of the myeloid variety which lasted two years. All the cases which last

more than a few months are of the myeloid type, chronic lymphatic leukemia apparently not occurring in childhood. Case 9 in our series died after an illness of ten months. This, like Case 20, however, was an atypical one in which, as we shall point out later, a stage of grave anemia without a leukemic blood picture preceded the stage of lymphocytosis. It must also be emphasized that cases like the above are prolonged by transfusion and radiotherapy. Occasionally the entire course of illness is limited to a few days. Case 5, aged seven months, was sick only four days. It is, of course, true that these brief periods of illness may be preceded by symptoms or blood changes not noticed by unobservant parents.

The course of leukemia undoubtedly resembles that of an acute infectious disease. Fever was present in almost every case, and was often the first symptom to be noted.

In this connection the article of Gordon Ward is of interest.[1] The author has collected and grouped 1457 cases of leukemia and has examined these in reference to their resemblance to acute infections. His conclusions are: "(1) There is a congenital form of leukemia which occurs in children whose parents are not leukemic. (2) Leukemic parents have never been known to transmit the disease to the newborn child. (3) Instances in which the actual infection of one person might seem to have occurred are very few, although not devoid of significance. (4) In having a marked preference for a particular age and sex, leukemia differs from the infective class of diseases and resembles the metabolic diseases and cancers." For these reasons the author believes the disease is not an infectious one.

That the leukemic blood picture may develop in the course of an infection is known, and it is naturally difficult to decide whether the leukemia is an added condition or part and parcel of the infection. As an example of the development of the lymphocytosis late in the illness, consider Case 20, whose detailed history follows:

R. B. (Med. No. 196608), aged four years, was admitted to the hospital November 17, 1919. He was one of five children. The four other children were living and well. The family history was negative. The boy had never before been ill and had had none of the acute diseases of childhood.

The present ailment had commenced suddenly one month before with chills, high fever (104°) and a purpuric eruption on the trunk. These symptoms subsided after a week, the rash gradually fading nad leaving only a yellowish discoloration. One week later the boy began to have very severe abdominal pain unrelated to meals and accompanied on three occasions by vomiting. At the same time he developed severe pain in his ankles and legs. These symptoms all

[1] British Jour. Dis. Children, January, 1917.

subsided until three days before admission, when the fever and abdominal pain returned and the purpuric rash again appeared, especially on the face. No blood was noted in the stool or vomitus. There had been a marked loss in weight.

Physical examination on admission showed an extremely pale, weak, sick-looking child. Over both cheeks were purplish-black ecchymoses which gave the boy a most grotesque appearance. On the arms, buttocks and legs were numerous hemorrhagic spots varying in size up to that of a twenty-five-cent piece. There were a few moderately enlarged, tender lymph nodes in the groins, axillæ, neck and the epitrochlear regions. There was a short, rough, systolic murmur heard along the left border of the sternum. The liver was felt one finger below the free border of the ribs and the spleen three fingers below. There was a small ulcer on the left anterior faucial pillar. Retinoscopy revealed numerous retinal hemorrhages. The urine examination was negative. The blood count was as follows:

Hemoglobin, 18 per cent.

Red cells, 1,200,000. Slight poikylocytosis and anisocytosis.

White cells, 1800.

Differential count: Polynuclear neutrophiles, 27 per cent; lymphocytes, 64 per cent; eosinophiles, 0; basophiles, 0; transitionals, 1 per cent; myelocytes, 2 per cent; metamyelocytes, 6 per cent.

Platelets, 72,000.

Coagulation time, 9 minutes.

Bleeding time, 2½ minutes.

Fragility of the red cells begins at 0.4 and there is complete laking at 0.325.

Von Pirquet and Wassermann tests negative.

At this time the diagnosis of aplastic anemia was suggested. The extremely low cell counts of both the red and the white cells pointed to a severe hypoplasia of the bone-marrow. Purpura hemorrhagica was another diagnosis suggested, in view of the hemorrhages, the diminished number of the blood platelets and the profound anemia.

Several transfusions of citrated blood obtained from the child's mother apparently caused a considerable improvement in the boy's condition, the hemoglobin rising to 32 per cent and the red cells to 1,912,000. The white cell count, however, at this time (two weeks after admission to the hospital) showed the following figures:

White cells, 4000;

Polynuclear neutrophiles, 4 per cent;

Lymphocytes, 86 per cent;

Large mononuclears, 10 per cent;

Subsequent counts confirmed these findings.

The interpretation of this cell count showed that the case was in

reality one of lymphatic leukemia, the diagnosis being based on the relative and absolute lymphocytosis. The low total white cell count does not militate against this diagnosis, for many cases are now on record in which the so-called aleukemic blood picture is found in the course of leukemia.

This particular case developed an abscess of the cheek, due to the breaking down of one of the hemorrhagic areas. This caused a retrogression in the progress which had been made, and when the child was taken home against advice the blood count had changed to: Red cells, 880,000; hemoglobin, 18 per cent; white cells, 2600.

This case is of interest in demonstrating how difficult it may be to make the diagnosis of leukemia in the absence of a characteristic blood picture. It is, of course, important to decide the diagnosis for prognostic reasons, since we know that all cases of leukemia in children are almost without exception fatal.

The above case is very closely resembled by one reported by Gunewardene.[2] A boy, aged three and a half years, showed a red cell count of 760,000, hemoglobin of 11 per cent and a white cell count of 8400. Polynuclear neutrophiles, 9.5 per cent; lymphocytes, large and small, 85 per cent; hyalines, 2 per cent; myelocytes, 2 per cent. This case was diagnosed as one of aplastic anemia, but when, after a remission, skin nodules appeared with many myeloblasts in the blood the diagnosis of leukemia was entertained. The postmortem examination showed myeloblastic changes in the bone-marrow.

To recur to the aleukemic blood count it is of interest to note that the white blood cells in our group of cases varied from 1400 to 720,000. In 9 cases the count on entering the hospital was above 50,000; in 7 it was between 11,000 and 50,000; in 2 it was between 5,000 and 10,000; and in 3 it was below 5000 cells. In several cases great changes took place in a few days. In some cases this was apparently due to roentgen therapy (Cases 16 and 17). The criterion of leukemic blood is the presence of abnormal cells in the circulating blood or a very definite change in the distribution of the normal cells. Apparently aleukemia is not a disease entity, but merely a stage in the course of the disease leukemia.

As we mentioned at the outset the lymphatic form of leukemia is much more common than the myeloid in childhood. In the present series the proportion is 20 of the lymphoid to 3 of the myeloid. It is, however, possible that some of the cases of lymphatic leukemia occurring in the earlier part of our series would now be classed as myeloid, owing to the recognition of the myeloblast cell which may easily have been mistaken for a lymphocyte. This cell, which is one of the progenitors of the myelocyte, is a mononuclear cell, the nucleus of which shows a finely reticulated structure, with

[2] British Jour. Dis. Children, January-March, 1920.

prominent nucleoli, and cytoplasm, non-granular, confined to a narrow peripheral zone. Naegeli[3] points out that the more acute the disease the more does this unripe type of cell displace the myelocyte. The acute myeloid leukemias, the existence of which was at one time doubted, are therefore accompanied by the extrusion into the blood not only of myelocytes but also of myeloblasts, sometimes almost to the complete exclusion of the former. Such cases often run an extremely acute course. Of this type is our Case 11, in a child, aged three years, showing 160,000 white cells, of which 57 per cent were myeloblasts. Such cases are usually accompanied by a very grave anemia and the presence of many abnormal red cells in the blood. Case 11 showed a red cell count of 1,480,000 with 21 per cent hemoglobin. The entire course of this case lasted four weeks.

In contradistinction to this form I would call attention to Case 22. A girl, aged eight years, previously in good health, began to complain of loss of weight and anorexia one year ago. Since that time she had been growing progressively weaker. Two months before entering the hospital an irritating cough had developed and continued. On admission, examination showed a pale, sallow, undernourished child, moderately dyspneic. All the superficial lymph nodes, but especially the cervical and submaxillary, were enlarged, hard and discrete. The left chest showed physical signs of a large pleural effusion. There were no enlarged superficial veins. The liver was felt 14 cm., the spleen 15 cm. below the free border of the ribs. Neither organ was nodular nor tender. The blood examination showed: Hemoglobin, 41 per cent; red cells, 2,080,000; white cells, 134,400; lymphocytes, 15 per cent; polynuclear neutrophiles, 5 per cent; myeloblasts, 80 per cent. The urine was negative. The temperature ranged from 99° to 101.5.°

The chest was aspirated twice but refilled rapidly. The pleural fluid was sterile, contained relatively few cells and had a specific gravity of 1012.

Clinically this case was one of chronic leukemia, though from the blood examination one would expect an acute history. Dr. N. Rosenthal, the hematologist at the hospital, was inclined to consider this case an acute one in spite of the history, believing that the leukemic process had been recently engrafted upon an old infection. The fact that myelocytes were entirely absent in the blood led us to exclude a so-called myeloblastic crisis, in the course of a myelogenous leukemia; for in such cases, notwithstanding the fact that great numbers of unripe cells (myeloblasts) are poured into the circulation there are present a certain number of maturer cells, myelocytes.

In this case then the blood findings pointed to an acute condition,

[3] Leukæmie und Pseudoleukæmie, 1913.

whereas the large, hard spleen and liver, the very large lymph nodes, the duration of symptoms and the slight fever were all in favor of the chronic type of the disease.

Of further interest was the hydrothorax. Radiograms of the chest taken before and after aspiration of the fluid failed to show any intrathoracic masses that might account for the pleural effusion. This is in accord with the findings in the other cases of our series in which chest radiograms have been taken. Apparently involvement of the intrathoracic nodes is rare, even in the chronic cases. These are quite contrary to the findings in cases of Hodgkin's disease, where, as pointed out by Wessler and Green[4] the bronchial and paratracheal nodes are regularly involved.

The participation of the nervous system in the leukemia of children is of considerable importance, and more attention should be directed toward it. In the present series Cases 5, 11, 12 and 23 showed involvement of the brain.

Case 5 was an infant aged seven months, admitted to the hospital July 26, 1915, in a moribund condition. The child had been taken ill four days before admission with restlessness, fever, a hemorrhagic eruption over the neck and shoulders and great prostration. Physical examination showed a dying child, extremely pale, with a hemorrhagic eruption, greatly enlarged liver and spleen and signs of meningeal irritation. The infant died before a careful examination was possible. Autopsy findings showed the lesions of acute leukemia, with a large hemorrhage over the surface of the brain.

Cases 11, 12 and 23 were all typical cases of acute leukemia which ended fatally with convulsions, delirium and coma. In two of them (11 and 23) lumbar puncture gave evidence of recent hemorrhage into the cerebrospinal fluid. The fluid was sterile.

In some cases the very first symptom of the disease is a convulsion. Such is a case seen by me, but not included in this series: An infant was brought to the hospital in coma, having been ill two days with high fever and convulsions followed by unconsciousness. Examination revealed an extremely pale child with numerous petechial spots scattered over the legs and trunk. There were a few enlarged lymph nodes in the neck. The spleen was not felt. On account of the fever, petechiæ and convulsions the case had been diagnosed as one of acute cerebrospinal meningitis, although all the classical signs of meningitis were absent. The lack of signs of meningeal irritation and the extreme pallor led me to diagnose a probable acute leukemia with cerebral symptoms. Lumbar puncture was performed and normal fluid under slight pressure was obtained. The differential blood count revealed 99 per cent lymphocytes.

Quite recently a similar case in a girl, aged seventeen years, has

[4] Jour. Am. Med. Assn., No. 7, vol. lxxiv, p. 445.

been reported by Munro[5] under the heading, "Acute Myelogenous Leukemia Simulating Meningitis." Here symptoms and physical signs of meningeal irritation were present. The acute illness lasted but ten days and was ushered in by headache, fever and delirium, which passed to a stage of coma, during which there were present rigidity of the neck, positive Kernig and Babinski signs, mild opisthotonos, a slight external strabismus and twitching of the right side of the face. Lumbar puncture yielded blood-stained fluid under increased pressure, smears and cultures failing to show any organisms. The blood count showed the findings of acute myelogenous leukemia. Postmortem examination failed to reveal evidence of inflammatory condition or gross hemorrhage anywhere in the central nervous system. The vessels of the meninges were markedly engorged and an acute edema of the brain and cord was present. The cord and cerebellum showed infiltration with mononuclear cells. The meningeal symptoms were here not due as in the first case to hemorrhage, but apparently to acute congestion and microscopic leukemic infiltration.

Leukemic infiltration in the brain may, moreover, affect considerable areas before causing symptoms. In a case diagnosed as septic diphtheria in a girl, aged fifteen years, upon whom I performed an autopsy, large brick-red masses varying in size up to that of a cherry were found scattered through the cerebrum. These masses proved to be deposits of leukemic tissue. The girl had died in coma, having shown no cerebral symptoms until a few days before death.

Tapie and Cassar[6] in an article on the nervous complications in leukemia comment on the fact that leukemic infiltration of the nervous system may be present without causing any symptoms whatever. In their article, which contains a very good review of the literature bearing on this subject, they report a case of hemiplegia due to capillary hemorrhage and leukemic infiltration of the internal capsule. They classify the nervous lesions which may occur in leukemia under the following heads:

1. Medullary degeneration: small foci of sclerosis or capillary hemorrhage in the brain or cord.
2. Leukemic infiltration: this may or may not cause symptoms.
3. Hemorrhages in nerve centers.
4. Nerve lesions due to compression.
5. Zoster.

To summarize my own experience, I have seen 6 cases of leukemia in children in which symptoms referable to the nervous system were prominent. Four of these gave the picture of cerebral hemorrhage. Three were proved cases: 1 by postmortem examination, 2 by lumbar puncture. The fourth case neither came to autopsy nor had a puncture performed; from its clinical picture, however,

[5] Jour. Am. Med. Assn., No. 9, vol. lxxiv, p. 603.
[6] Arch. de mal. du cœur, 1919, xii, 218.

cerebral hemorrhage could with probability be diagnosed. I have described a case of acute leukemia mistaken for cerebrospinal meningitis, the clinical findings of which pointed to a leukemic infiltration as the cause of the symptoms. A very similar case with autopsy is reported from the literature. Finally, I have described a case with terminal cerebral symptoms in which areas of macroscopic leukemic infiltration were found at postmortem examination.

I wish to express my indebtedness to Dr. Henry Heiman for permission to make use of the material from the pediatric service of Mount Sinai Hospital.

PERICARDITIS: INCIDENCE AND DIAGNOSIS.[1]

By W. W. G. Maclachlan, M.D.,
ASSISTANT PROFESSOR OF MEDICINE, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Inflammation is prone to develop in the serous sacs of the body, in some, seemingly, more than in others. The inflammatory reactions demonstrate nicely the various types of inflammations; in fact, in no situation in the body is one able to observe a more distinct set of reactions than are met with in the different forms of serositis. With the exception of direct wounds, infection in serous sacs is always a secondary manifestation of some primary focus, even though, at times, this focus may be so completely hidden as to escape recognition. One usually does not regard epidemic meningitis exactly in this light, but really the invasion from the upper respiratory tract of the meningococcus with a subsequent meningitis or of the Streptococcus salivarius with its accompanying arthritis or pericarditis is theoretically the same. There is no reason to believe that serous sacs are not infected in the usual ways—namely, by the blood stream, the lymphatics or by direct extension. It is, however, impossible in some instances of pericarditis to be certain of the manner of infection, hence the term idiopathic has been applied to certain clinical forms of the disease. On general medical grounds this term is a poor one, and even though, from the point of view of proof, it is at times correct, still it is probably better to drop the word idiopathic. The pericardium is subject to four types of acute inflammation; the acute fibrinous and the serofibrinous are the common forms while the purulent and the hemorrhagic forms are less frequent. The chronic inflammations are indicated by fibrous adhesions, localized or general in distribution, and a rather unusual form in which a diffuse thickening of the pericardium is observed. Tuberculosis produces an inflammatory reaction which

[1] Read at the Interurban Clinical Society, Clifton Springs Sanatorium, October, 1920.

at times shows characteristics typical of both acute and chronic inflammation in addition to the granulomatous reaction.

It is quite apparent from clinical and pathological observations that the different serous sacs are by no means numerically equally involved in infection. There is no reason to believe that any inherent variability in the power of the resistance is possessed by one and not by the other. It would seem, rather, that the anatomical position in the body on the one hand and the type of bacterial infection on the other suggests the explanation. For example the acute inflammations of the peritoneum are practically always purulent, because they are secondary in most instances to a ruptured or leaking hollow viscus containing pus-producing bacteria. The pericardium, however, has choicer surroundings as the rupture of a viscus into it is extremely unusual; while, further, the Streptococcus pyogenes is not the prevailing organism in inflammations of the chest, the possible regional source of pericarditis. On the other hand the frequency of pericarditis in the Streptococcus viridans infection and the infrequency of any peritoneal involvement by this organism, at least that can be recognized as such, would appear to indicate that the type of bacterium is a factor of importance in inflammations of serous membranes. In the same way, Streptococcus viridans infection of the meninges, except in an occasional case of chorea, is very unusual; but it undoubtedly occurs in the pleura. It is not our purpose to become entangled in the bacteriological question of specific localization of bacteria which, in a certain sense, is correct as the localization of the meningococcus in the meninges, the tendency for Streptococcus viridans to be present in carditis, while the absence of these bacteria in the peritoneum certainly would suggest specificity in location. This, however, under no condition means that Streptococcus viridans isolated from a pericardial sac will always produce a pericarditis. Holman, McMeans and others have settled this point. The prevalence, therefore, of acute fibrinous or serofibrinous inflammations in the pericardium would appear to be due, firstly, to the fact that the most frequent bacterial invader is the Streptococcus viridans, and, secondly, the pericardium is not especially subjected to the influence of the usual pus-producer, the Streptococcus pyogenes. That the pericardium is readily available for a purulent infection if the pus-producing organism is present, is clearly shown by the considerable number of purulent pericarditis cases found in streptococcic pneumonias and to a lesser extent in the pneumonia of pneumococcic origin.

It is my purpose to deal with the pericardium in inflammatory conditions as recognized at the bedside and at the autopsy table. It must be kept in mind that acute pericarditis, with or without effusion, has not a high mortality and therefore the cases that come to autopsy, dying from acute pericarditis *per se*, are unusual. Further, much of the acute pericarditis found at autopsy is but a

terminal part of the picture of infection in that individual. Chronic pericarditis is of interest in indicating the number of cured acute forms and also in calling attention to clinical difficulties of diagnosis in this condition, for it still seems to be a fact, as Osler remarked many years ago, that chronic pericarditis is more often found in the autopsy room than in the ward. I thought it would be of some interest to review our autopsy records on this subject and to collect from them any data which seemed to have a pertinent bearing on the subject of pericarditis.

The subject of pericarditis is an old one, and in the literature it has been thoroughly covered as the reports, which are legion, on this disease would indicate. Our pathological findings are in accord with what has been shown in the past, our figures bearing a striking resemblance to those published about twenty years ago by Wells. One is also forced to say there is little further to add to the diagnosis; but as we are still going to have pericarditis with us it is possibly not out of place to occasionally submit a review. The number of autopsies examined was 975; in 100 of these pericarditis was present in some form. For the opportunity to study these records and for the helpful discussion with reference to them I wish to thank Dr. Oskar Klotz.

There are two conditions to which brief reference should be made, although neither of them is classed under inflammation. Hydropericardium has clinical significance in that some degree of this transudation is present when edema is a characteristic of certain chronic diseases, especially nephritis and primary anemias. A well-marked increase of fluid in the pericardial sac without other signs of pericarditis, or the presence in the body of edema in the tissues or fluid in the cavities, should be held in suspicion as probable evidence of the inflammation, the reaction being principally of a serous character. This differentiation, however, does not appear to be a difficult problem to decide, either from the clinical or the pathological point of view. A milk spot on the surface of the heart is, to say the least, a rather common finding. About the origin of these spots there is considerable debate, as the question has been raised as to whether they represent the end-results of inflammation or merely the effects of long-continued rubbing of the pericardial surfaces. It is not my intention to attempt to settle this problem in one way or the other, notwithstanding the fact that I have observed at least some milk spots to be of an inflammatory nature. They occur at all ages. Our records show 2 examples in infants, but they are undoubtedly more common past the middle period of life. It seems rather strange that we should not know exactly why these plaques develop as they are certainly accessible to study.

Under this heading we have the acute fibrinous, serofibrinous and purulent forms of pericarditis. The first two types predominate; gradations in the purulent forms occur from the slightly turbid

fluid to a frankly purulent one. The latter type has been unusually infrequent in our series of cases. There are several points brought out in the table which would bear some analysis. It is at once seen that a little over 5 per cent of the autopsies showed an acute pericarditis, and of this number the males were more than three times as numerous as the females, bearing out the general known sex incidence of this disease. Rather strangely, however, more cases occur after the age of forty. This is likely due to two facts, the number of children in our series was relatively small and acute pericarditis, *per se*, is not often fatal. It should be kept in mind that there is a difference in the group of acute pericarditis cases met with in the wards and in the autopsy room, especially in regard to the age. As a clinical disease, acute pericarditis is more often observed in young adults and children; further, it has a relatively low mortality, and hence is not frequently seen at autopsy. On the other hand, there are many instances of acute pericarditis appearing as a terminal infection with some other acute disease which was the cause of death. The involvement of the pericardium in this type of case is frequently not recognized before death; while it may be present at any age, our results indicated the tendency of this form to develop more often after middle life.

TABLE I.—ACUTE PERICARDITIS.

Cases.	Sex.		Age.		Amount of fluid.	
50	Males	39	up to 10	2	5 c.c.	1
	Females	11	10 to 20	6	10 c.c.	1
			20 to 30	7	15 c.c.	1
			30 to 40	9	20 c.c.	2
			40 to 50	10	50 c.c.	12
			50 to 60	7	60 c.c.	1
			60 to 70	8	70 c.c.	1
			70 to 80	1	100 c.c.	5
					150 c.c.	2
					200 c.c.	2
					300 c.c.	1
					400 c.c.	1
					600 c.c.	1
					Stated as not increased	19

Acute pericarditis does not necessarily produce an increase in the amount of fluid in the pericardial sac. Almost three-fourths of our cases showed 50 c c or less fluid in the sac, while but one-seventh of the number had more than 100 c c of fluid present. This would seem to indicate, from the autopsy point of view, that the majority of acute infections in the pericardium are not associated with a large amount of fluid; but, as we mentioned previously, it is well to keep in mind that the acute serofibrinous pericarditis seen in the younger individual rarely comes to the autopsy table by reason of that disease alone. The reliance on increased cardiac dulness, assuming that it is due to fluid, as a point of diagnostic value may

not have an anatomical basis; in fact, I seriously doubt that it is possible to recognize with any method of physical examination an amount of fluid less than 100 cc. In only one-seventh of the cases, therefore, would the amount of fluid present have been of diagnostic aid.

One is not always able to demonstrate the etiological factor of this disease. It is our impression that acute rheumatic fever, chorea and tonsil infection with the endocardial and myocardial complications account for the majority of our acute clinical pericarditis. Streptococcus viridans infection is closely associated with this group, whether as the primary infecting agent or not, it is difficult to say, but certainly it is a factor; eliminate this streptococcus and there is nothing left. Until proved otherwise let us regard this infection as the etiological one for this group. Our actual findings, however, would indicate that acute endocarditis was present 10 times with acute pericarditis; but on 32 other occasions no pericardial lesion was associated. This merely shows that endocarditis is the more common lesion of the two. On 6 occasions during the acute stage of rheumatic fever with arthritis and twice associated with acute chorea a pericarditis was found, and in all of these instances there was other cardiac involvement. Two acute infections of the throat in chronic heart and kidney disease completes the list of this etiological group, comprising thus two-fifths of the cases.

It was somewhat surprising to find that in 128 cases of lobar pneumonia there were only 10 associated with pericarditis, and in one-third of these the inflammation was purulent. It is of interest to remember that a considerable amount of suppurative pericarditis was found in the pneumonias of streptococcic origin; but this bacterial finding has been practically unknown in the lobar pneumonia of our community. The pneumococcus seemingly is not especially prone to develop a pericarditis (7 per cent), but when this condition does occur it is liable to become purulent. In all probability if the duration of pneumonia were longer more purulent exudates likely would be found in the pericardial cavity. There were 13 other cases in which some inflammatory focus was present in the lung, as foreign body with mediastinitis, empyema, abscess and gangrene, tuberculosis and cancer; about one-half of these were of streptococcic origin. Suppuration in the pleural sac is certainly a commonplace complication of pneumonia as compared with pericarditis in the same disease. One case of pericarditis was present in 50 autopsies on epidemic influenza.

Infection arising from the peritoneal cavity, particularly from the gall-bladder with liver or subdiaphragmatic involvement, accounted for 7 cases of pericarditis. In this instance the infecting organism is almost always a streptococcus pyogenes.

Recently, Libman has called attention to the association of acute pericarditis with coronary embolism and infarction of the heart.

I have confirmed this on one occasion during the past few weeks and there is one other case in our records. This observation would bear further watching, as it may be of considerable value in diagnosis.

It was not possible to get an accurate estimate of the bacteriology, as certain difficulties were present which would have to be considered before laying too much stress on the autopsy bacteriological findings. To put any reliance upon these findings it is necessary to have the cultures made within as short a time as possible after death, as post-mortem contamination in the thorax occurs very quickly. In our opinion, however, the Streptococcus viridans and pyogenes are the two common invaders while the pneumococcus ranks next. A word possibly would not be out of place regarding the fibrin deposited on the pericardial surfaces. It is often present in very small amounts. The surface over the right ventricle and at the base between the larger arterial trunks appears to be the most frequent situation for fibrin, especially when it is very sparingly distributed. In this connection it is of interest to remember that this is also the situation (anterior wall of right ventricle) favored by milk spots to which we previously referred. One has often to look carefully to see the fibrin on the surface of the right ventricle even where in life a well-marked friction sound had been heard. I have had the opportunity of following this point in several cases within the past year, and must admit being surprised to find so little fibrin in certain instances where very definite friction rubs had been present.

TABLE II.—CHRONIC PERICARDITIS.

Cases.	Sex.		Age.		General adhesions.	Local adhesions.
40	Males	31	Up to 10	1	17	23
	Females	9	10 to 20	5		
			20 to 30	9		
			30 to 40	10		
			40 to 50	5		
			50 to 60	6		
			60 to 70	2		
			70 to 80	2		

The presence of fibrous adhesions in the pericardial sac indicates a chronic pericarditis. These adhesions may be localized as a few fine fibrous strands more often noted at the base of the heart, but also present anteriorly near the apex; or they may be diffusely present, forming the so-called general adhesive pericarditis. The localized fibrous adhesions in all probability in the majority of instances are little more than interesting pathological findings, as they are not only impossible to diagnose clinically, but there seems to be, further, little evidence to indicate that they actually produce any mechanical disturbance. Of course, a heavy isolated band in certain situations might produce considerable impairment in function leading to compensatory changes, as hypertrophy of the heart.

But these instances in our opinion are rather the exceptional findings. Table II shows that a little more than 4 per cent of the autopsies presented evidence of chronic pericarditis, and of this number a little less than half were of the general adhesive type. The male predominates, the relation being about the same as it is in the acute form of the disease. It is of interest to note that in one newborn child a diffusely adherent pericarditis was found. The infant presented some suggestive signs of congenital syphilis, although positive proof was never established. Over a half of the cases occurred under the age of forty, which is exactly opposite to what was found in acute pericarditis. The amount of fluid in the pericardial sac does not appear to have any relation to this form of pericarditis, as in the adherent form there is, of course, no fluid present, while in the localized type there is nothing in the adhesions themselves to call forth an effusion. It is my impression that one rarely sees chronic pericarditis with effusion, as this condition is either a persistent acute serofibrinous form or a tuberculous process. The latter is by no means rare.

It is a very difficult matter in many cases to identify the etiological factor responsible for chronic pericardial adhesions. This is but to be expected, as fibrous adhesions indicate an end-result, and it is always difficult to follow the course of a disease, especially pericarditis, a disease so often of an indefinite character. As a general principle, it would seem to us that the best explanation for the production of chronic adhesions is the organization of an acute fibrinous pericarditis and, therefore, the etiology would be the same for the chronic as for the acute form. Wells has suggested that a certain number of the adherent types of pericarditis are of a tuberculous nature, many possibly never existing in the state of a tuberculous pericarditis, but representing the fibrous tissue reaction induced by the tuberculous toxin developing in an adjacent active lesion such as the mediastinal lymph nodes. According to Wells the adhesive forms show nothing which would indicate tuberculosis either in the gross or in sections. We agree with this statement. It is possible that some obliterated pericardial sacs develop in the way suggested by Wells, but it is our impression that they form only a very small percentage of these cases. In but 3 of our 17 cases does it appear likely that tuberculosis was the etiological factor. At least it was the only disease present, the heart being perfectly normal. It should be added that there was nothing in these 3 cases in the pericardium itself to indicate morphologically a lesion characteristic of tuberculosis. According to our records this form of pericarditis is more often associated with endo- and myocarditis or what we may term the rheumatic-fever-cardiac group. This, in our opinion, is the etiological factor of first importance for any form of chronic pericardial adhesion but actual proof of this is not always forthcoming. That the other acute infections, as pneumonia, play

a part is but logical. There is nothing to indicate why general pericardial adhesions develop in some instances and local adhesions in others, although it would seem most likely that a massive acute inflammation would be more prone to develop general adhesions. On the other hand, however, it is quite possible that a recurrent infection could produce the identical result; while localized adhesions most likely would indicate single infections, probably not of an intensive character. As these are points which, even at the best, are debatable, one should not lay too much stress upon them.

Heart changes are not always associated with chronic pericarditis, and *vice versa*, pericarditis is not always present in heart disease; the endocardium and myocardium are undoubtedly more vulnerable than the pericardium. This fact is brought out in our records which show no pericardial involvement in 43 autopsies in which the cause of death was due to heart disease. In 11 of the chronic adhesive pericarditis cases there was evidence of chronic endo- or myocarditis, thus leaving 3 cases of this type in which the etiology was most indefinite, as tuberculosis was not present. The relation of kidney and arterial disease to chronic pericardial changes is approximately the same as that of the heart, in that these three vital structures are so commonly associated in disease. The actual size of the heart does not appear to depend entirely upon mechanical difficulties thrust upon it by an adherent pericardium, as there were several instances with little or no cardiac hypertrophy. Enlargement of the heart in this condition is seemingly related more to the myo- or endocardial changes, to nephritis with hypertension or to extensive adhesions to the adjacent structures outside of the pericardial sac. There were no typical examples of Pick's disease in our series.

TABLE III.—TUBERCULOUS PERICARDITIS.

Cases.	Sex.		Age.	
10	Males	9	Up to 10	0
	Females	1	10 to 20	2
			20 to 30	3
			30 to 40	2
			40 to 50	2
			50 to 60	1

In this table one sees again the predominance of the males in pericarditis and it further indicates an earlier age level, as three-fourths of the number were met with before the age of forty. Tuberculous pericarditis usually produces a very large sac, containing a great deal of fibrin and often a large amount of fluid. This fluid may be blood-tinged, but more often it is clear and straw colored. The largest pericardial sacs, according to our records, have been the tuberculous ones. One rarely sees at autopsy the development alone of miliary tubercles on the pericardial surfaces in the same manner as one observes them in the pleura. Certainly, there is probably

a stage in the development of tuberculous pericarditis when it is likely that only tubercles are present; but the production of fibrin is soon so extensive that, at first glance, the characteristic appearance is that of an acute fibrinous pericarditis. At autopsy this fibrinous character is always evident, and it is by no means improbable that a certain number of tuberculous pericarditis cases are labelled acute fibrinous pericarditis. The tubercles are readily enough seen when the fibrinous exudate is scraped off so as to expose the deeper layers, and once in a while it is necessary, when the tubercles are indistinct, to wait for a microscopic section in order to be quite sure of the diagnosis. The term bread-and-butter heart may apply equally well to both the acute fibrinous and the tuberculous forms of this disease. At times one sees in the deeper portions of the exudate the development of a moderate amount of caseation, although this feature has not been prominent in the materials which we have studied.

The question has been brought up as to whether some of the diffuse adherent pericardial sacs represent healed forms of tuberculosis. Although this is a possibility it is my impression that such a fortunate sequence of events rarely occurs. The healed tuberculous lesions of the pericardium which present unmistakable signs of this disease are extremely unusual if one is to consider calcification as an evidence of healing. Wells observed calcification on 4 occasions, but he is inclined to look upon this deposit as being secondary to a suppurative condition in the sac. We did not see any example of calcification in our series, but agree with Wells that this change and probably also what has been described as calculi in the pericardial sac represent the end-result of a purulent pericarditis. Calcification following chronic empyemas secondary to lobar pneumonia with tuberculosis ruled out at autopsy, in which a cast of the chest wall had formed, have occurred several times in our records. So by analogy it would appear that the same process is possible in the pericardial sac. We mentioned before Well's conception of the relation of tuberculosis to certain of the adhesive forms of chronic pericarditis. He admits that it is a difficult thing to prove, and we follow him in this matter.

A similarity of origin is quite possible between adherent pericarditis and chronic adhesive pleuritis. It is the general conception that tuberculosis is the most common productive factor in this latter condition, although by no means the only factor. Anatomically these adhesions represent nothing but fibrous tissue, and only rarely is one able to demonstrate in them histological evidences characteristic of tuberculosis. There is, therefore, some ground for considering chronic adhesive pericarditis as having a tuberculous etiology, but as we have seen this condition associated more often with the rheumatic group it is our impression that tuberculosis accounts for but a minimum number of these cases. It would be interesting to observe

the final result in the cases of tuberculous pericarditis which have been apparently cured by drainage of the sac. My experience with this disease has led me to regard it as a very severe form of local tuberculosis possibly as malignant as its kindred infection of the meninges.

The relation of pericarditis to tuberculosis elsewhere in the body is of considerable interest. It is in fact always a secondary infection. There was only one case in which we were unable to find the primary focus of tuberculosis, but this by no means indicates that the pericarditis was the primary disease; it merely shows that the original focus was probably very small, likely a hidden lymph node lying so close to the pericardium that it could not be clearly identified. A point of considerable interest is that the development of a tuberculous pericarditis seems to have little relation to the extent of the tuberculous process elsewhere. In other words this disease in the pericardium is often purely a local entity in the same way as tuberculosis of the peritoneum or meninges. Remembering how prone endothelial lined cavities are to involvement in a process of general miliary tuberculosis, it was of interest to record but 3 cases where a pericarditis was present in this general infection. The pleura, peritoneum, meninges and solid organs may be studded with tubercles and yet the pericardium escape; while, on the other hand, a marked pericarditis may be present with only the mediastinal lymph nodes presenting the primary lesion. It appears to us that tuberculous pericarditis has a more intimate etiological relationship to tuberculosis in the mediastinal lymph nodes than to this disease in any other situation, and that the infection is lymph-borne or possibly by direct extension. This view is in agreement with what has been previously expressed by many writers on this subject. A blood-stream infection in general miliary tuberculosis does occur, but this we regard as the rare method of infection of the pericardial cavities. In only 5 cases out of a total of 37 dying of pulmonary tuberculosis was there any evidence of a tuberculous pericarditis. This would seem to indicate that the pericardium very often escapes even in fatal forms of tuberculosis of the lung. As latent or healed tuberculosis of the lung is such a common finding, its relation, therefore, to the pericardium must be practically *nil*. As was just stated, in 3 instances of general miliary tuberculosis there was a tuberculous pericarditis, but in 20 others, comprising miliary tuberculosis of the peritoneum, meninges, pleura and bowel, the pericardium was negative. Both the peritoneum and the meninges are more often involved while the pleura is rarely missed in a tuberculous death.

Diagnosis. *Acute Pericarditis.* Pericarditis is often not diagnosed, as the clinical record of any service, where autopsies are made with moderate regularity, will show. It is no doubt a difficult diagnosis to make in many cases. Further, some of the very recent

inflammations of the sac found at autopsy are probably of relatively few hours' duration, hence they could be very easily missed. It is also possible and probable that some of these infections do not give any physical sign. At the same time, however, we are quite certain that many acute pericardial cases which are unrecognized, at some stage of their course do present the classical signs, and if one is on the watch for this disease, positive results will be more often forthcoming. We have nothing new to add to the method of diagnosis; the symptoms and signs have been described in detail in text-books and in numerous articles.

In the diagnosis of acute pericarditis the friction rub is by far the most important sign. We do not need to go into its character or its situation, but suffice it to say that the to-and-fro grating sound, heard usually outside of the left sternal border below the third rib, is pathognomonic of a fibrinous pericarditis. The rub may be localized to an area not larger than the end of the stethoscope or it may be well heard over the whole of the precordium. Cessation of breathing and slight pressure on the end of the stethoscope are aids in bringing out this murmur. Its demonstration is worth all of the other symptoms and signs combined. The fleeting character of the friction sound should be kept in mind, as it may be present when the intern makes his night rounds and yet be absent when he attempts to demonstrate it to his chief in the morning. This is the reason why careful and frequent observations are essential if we are going to recognize the majority of the acute fibrinous pericarditis cases. I am not sure that the development of fluid is the only reason to explain the disappearance of the friction rub. It is possible that where very little fibrin has formed, absorption may readily occur. A very loud rub can be produced by an unusually small amount of fibrin, so small, in fact, that it may be readily missed by a careless gross inspection of the heart at autopsy. The next sign of value appears to be the size of the cardiac dulness. The increased dulness is due to the presence of fibrin or fluid, or both. One must keep in mind, however, that an increase of fluid is by no means a regular finding in acute pericarditis. Half of our cases had less than 100 c c, and I doubt very much that this amount could be appreciated by physical examination. Possibly as small an amount of fluid as this might be recognized by a roentgen-ray plate or fluoroscopy. Where larger amounts of fluid are present the well-known pear-shaped cardiac dulness can be readily demonstrated by percussion, but we should always confirm this with roentgen-ray examination. This form of pericarditis with its sudden onset and rapid accumulation of fluid, as shown by the increase in the cardiac dulness, can be readily followed in its development. Associated often with this rapid distention of the pericardial sac, one may observe cyanosis and dyspnea accompanied by pain.

The change in the intensity of the cardiac sounds from the very

distinct to the faint or muffled character, as the fluid and fibrin accumulates can, at times, be observed, and when present is of great value.

The presence of the precordial pain, associated with a febrile condition and an increased pulse-rate, is seen in about a third of the cases. McKenzie believes that all pain accompanying acute pericarditis is a manifestation of myocardial involvement, as the lesions of the pericardium itself are painless. This is a very interesting point, and may be the explanation, although McKenzie in his typical way does not force us to accept his conclusion. Might it not also be possible to explain the pain in some cases of pericarditis as being due to an associated involvement at the base of the aorta? Klotz has called our attention to the fact that an aortitis is not an infrequent sequela of an acute rheumatic fever. As it is following this disease that most of our acute clinical pericarditis develops, it would seem reasonable to believe that aortitis, which is very often painful, may share with the myocardium as being the source of this important symptom. There is one other explanation to be considered: the sudden stretching of any moderately rigid sac is liable to cause pain, and, therefore, in those cases of acute pericarditis associated with the rapid accumulation of fluid the presence of pain may be due to the stretching of the pericardium. This, however, does not appear to apply if enlargement of the sac has not been brought about rapidly, for we have seen enormous pericardial sacs in tuberculous pericarditis which clinically were quite devoid of any suggestion of pain. These accumulations, however, are always of a more gradual development.

There are many other minor signs described, but it is unnecessary to repeat them here, as Robey has recently written on this matter in detail, to which work the reader is referred.

Chronic Pericarditis. The diagnosis of chronic pericarditis is a very difficult one to make, much more so than the acute form. It may, in fact, be impossible to recognize this condition. We can see no clinical method which could possibly help us to diagnose local isolated fibrous adhesions. This form of pericarditis is purely an autopsy finding, but where the adhesions are general, or massively developed at one point, they may produce in a certain number of instances signs by which they can be recognized. In view of the fact that some cases of general adhesive pericarditis are found at autopsy without evidence of their having produced any change in the gross appearance or function of the heart, it can be readily seen that there are difficulties ahead when one attempts to speak on the diagnosis of chronic adhesive pericarditis. There are no pathognomonic signs or symptoms of this condition, but there are some suggestive points which when present, are of value, but their absence is not of much significance in ruling out adhesive pericarditis.

The retraction of the lower ribs, posteriorly on the left side, with

cardiac systole (Broadbent's sign) is probably of most value in diagnosis although it must be kept in mind that this sign has been found in other conditions than adhesive pericarditis. The retraction of the lower end of the sternum and the pulling in of the costal margins in inspiration, as pointed out by Hoover, are at times noted. There are a number of other points that have been suggested, and possibly on certain occasions they are of value. The diastolic shock at the apex and the diastolic collapse of the distended veins in the neck have been given as signs of clinical worth, but I doubt if anyone would like to rely too much on such evidence. It is our impression that fluoroscopic examination of the diaphragmatic movements in a certain percentage of cases may offer some suggestive points of value. It might also be of importance in roentgen-ray examinations to lay more stress on the appearance of the mediastinal tissues which usually show some alteration when the pericardial sac is involved. No reliance is placed upon the quality of the heart sounds, but cardiac derangement out of keeping with the apparent valvular lesions has been advanced as possible evidence of adhesive pericarditis.

There is a point which I believe may be of great value in making this diagnosis, but it is neither a sign nor a symptom. To be able to prove without any question of doubt that the individual had a previous attack of acute pericarditis is of extreme value, and in our opinion may be the only factor present which would lead one to the diagnosis of adhesive pericarditis. We have but recently seen an excellent example of this very condition. Five years ago, in the medical ward, I observed a very extensive acute fibrinous pericarditis following an acute rheumatic fever and associated with an endocarditis and in all probability a myocarditis. The patient recovered and graduated as a male nurse a few years afterward. He was in good condition and worked regularly at his occupation. He had some suggestive signs of a mitral stenosis with regurgitation; the heart was hypertrophied, but the action was regular. In April of this year, five years after the original infection, he developed tonsillitis with an acute pleurisy and atrial fibrillation was recognized. It was not present a short time previous to this acute attack of infection. He made a perfect recovery from his acute conditions and after a month's rest had his tonsils removed under local anesthesia. He died suddenly a month later. At autopsy a general adhesive pericarditis with hypertrophy and dilatation of the heart and a slight thickening with but little stenosis of the mitral valve were found. There was nothing whatever in this case, in the way of physical sign, pointing to an adhesive pericarditis except that we known positively that some years previous he had an acute fibrinous pericarditis, and on this ground alone an adhesive pericarditis had been suggested along with the myo- and endocardial changes.

Tuberculous Pericarditis. The form of tuberculous pericarditis which we especially refer to is a serofibrinous exudate implanted

upon a tuberculous base. Some of the largest pericardial sacs and some of the best examples of the bread-and-butter heart are of this type. Clinically, tuberculous pericarditis very often proceeds as an individual process which early has the appearance of an acute pericarditis, but which later passes into the subacute or chronic form. In our experience they have all been fatal and not necessarily associated with marked or extensive tuberculosis elsewhere. In a chronic pericarditis with effusion one should always think of tuberculosis, and here, of course, it must clearly be understood that a hydropericardium is not to be mistaken for this condition. The diagnosis of tuberculous pericarditis is not always easy, and at times is made only at autopsy. The chief point in diagnosis is the chronicity of the process in a lesion which presents the physical signs of an acute serofibrinous pericarditis.

In the early stages the signs are like those of acute fibrinous pericarditis. The friction rub is usually well heard over a considerable portion of the precordium, and it often persists for a considerable period of time. On two occasions I have been able to hear the rub for almost a month. There is rarely any pain in this condition, although it may be present. A diffuse, persistent friction rub over the heart without the slightest evidence of pain, as is seen in many of those cases, rather supports McKenzie's statement that the pericardial sac is devoid of pain. As fluid is nearly always present, and at times in very large amounts, the cardiac dulness consequently is much increased. The presence of dulness behind at the left base is noted in this condition with some regularity. It is not diagnostic of the tuberculous pericarditis, as it may also be present in any type of sac containing a large amount of fluid. The change from day to day in the character of the heart sounds is of considerable value, and I have been able to follow this sign on several occasions from clear, loud cardiac sounds to those which became distinctly muffled. The accumulation of fluid and fibrin is responsible for this change in the heart sounds. The febrile reaction is of a tuberculous type. The pulse-rate is rapid, and as the disease advances the temperature elevations become greater and the rapidity of the pulse increases. The course is progressively downward.

Conclusions. 1. Ten per cent of our autopsies showed pericarditis; 5 per cent were acute, 4 per cent were chronic and 1 per cent were tuberculous.

2. The principal etiological factor, in the acute and chronic forms of pericarditis, seems to be associated with the disease acute rheumatic fever.

3. Acute pericarditis was present in 7 per cent of the acute lobar pneumonias. The majority of these appeared probably shortly before death. The streptococcus in thoracic infection is more prone to produce suppuration in the pericardial sac than the pneumococcus.

4. In 54 cases of death due to tuberculosis there was no evidence of tuberculous pericarditis.

5. Tuberculous pericarditis is usually of the serofibrinous variety; it may be present in the absence of other clinical signs of tuberculosis; pathologically there is always a primary focus, usually in the lymph nodes of the thorax or in lung. The pericardium is often missed in a general miliary tuberculosis.

6. Tuberculous pericarditis should always be considered when the signs of acute pericarditis persist for an unusually long time, and especially when there is considerable cardiac enlargement and a progressively downward clinical course.

7. The presence of a friction rub is the most valuable diagnostic sign of acute pericarditis.

8. Chronic adhesive pericarditis can be diagnosed only in a small percentage of cases, as there are no distinctive signs. It is of real value to know of a previous undoubted attack of acute fibrinous pericarditis when considering the possible presence of a general adherent pericarditis.

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BALANTIDIUM COLI AND PERNICIOUS ANEMIA: REPORT OF FOUR CASES.

By A. H. Logan, M.D.,
SECTION ON MEDICINE, MAYO CLINIC, ROCHESTER, MINNESOTA.

Balantidium coli is a flagellate parasite inhabiting the colon, common in animals, especially the pig, but rare in man. The work of Strong, Bowman, Bel and Couret, and Manlove, shows that the parasite is capable of invading all layers of the intestinal wall. It has been found in the bloodvessels of the intestine and in other organs. With the accompanying bacteria superficial and deep ulcers are formed which cannot be distinguished from ulcers due to ameba until the microscope differentiates the parasite. The parasite also possesses the power of encysting.

The clinical symptoms of invasion by *Balantidium coli* bear a great similarity to those produced by ameba. Both present an acute and chronic form. In the acute form there is severe bloody dysen-

tery, with great loss of fluid and marked toxicity. Perforation may occur. Death follows usually in from a few days to one or two weeks. The chronic form often exists for years with alternating constipation and diarrhea. As with many other parasites the acute form seems to develop chiefly in warm countries and the chronic form in colder regions.[10] The symptoms and findings of pernicious anemia seem to accompany the chronic form of the infection.

The prognosis in the acute type is very bad, even if the case is seen early. In the chronic type it seems to be bad only when the syndrome of pernicious anemia is added. Our patients have died from the pernicious anemia rather than directly from the dysentery.

Schwartz finds a hemolytic agent in *Ascaris lumbricoides* and *Trichuris trichiura*, which he believes accounts for the anemia in these infections. Under certain conditions, supposedly including a decomposition of the segments of the worm, *Dibothriocephalus latus* produces a picture of pernicious anemia. If the worm is expelled the blood picture returns to normal.

Glaessner has found a hemolytic agent in *Balantidium coli*. It seems probable that the constant subjection of the blood-forming organs to the poison is the cause of the pernicious anemia syndrome in the chronic type of case. The removal of the *Balantidium coli* and its hemolytic agent is a far different problem than the removal of the Dibothriocephalus latus. Since *Balantidium coli* penetrates the intestinal wall and its bloodvessels and other organs in the body and also encysts we cannot be sure when the organism is eradicated from the stools that it is not harbored somewhere in the tissues of the body with its hemolytic agent still active. Thus if the pernicious anemia complex persists after treatment we cannot be sure whether the toxin of *Balantidium coli* is still active or whether once the complex is started it becomes an entity.

The treatment resolves itself into ridding the intestinal lumen and the body tissues of the organism. The literature indicates that most of the drugs used against intestinal parasites are without effect on *Balantidium coli*. In our experience in the Clinic with the flagellate *Lamblia intestinalis* we found that the only drug that gave any satisfaction was put into the blood in sufficient quantity to act as a direct poison when ingested by the parasite; in a large number of cases arsphenamin proved of great value. In our latest case of infection with *Balantidium coli* we employed arsphenamin with apparently very good effect. An enema with vinegar and tannic acid also was given every day or every second day with the idea of producing an acid medium in the colon and of giving a direct parasiticide. On account of encystment the treatment must be carried out a long time, just how long I do not know, since the length of time the organism may remain encysted and become active again has not been determined. That the living organism is very resistant is shown by Klein, who found actively motile *Parame-*

cium coli in sewage which had been bottled for three weeks. In the case treated by five intravenous injections of arsphenamin at weekly intervals, nine stool tests were negative for the parasite, the diarrhea was entirely checked, and the patient felt very much better; yet the neurological symptoms of pernicious anemia still persisted. Jennings reports one case with the pernicious anemia syndrome which was apparently cured after two relapses.

It is interesting in connection with the family histories of three of our patients that death of one or more parents, brothers or sisters, persons in the same household living under similar conditions and eating the same food, occurred from pernicious anemia or anemia. This may explain the family tendency to pernicious anemia in many cases.

Case A52257, Mr. W. T. L., aged forty-two years, a farmer for the past five years, came for examination April 26, 1911. The patient had had a spell of diarrhea for two months when working in a butter and cheese factory twelve years before. The diarrhea had recurred off and on until five years before, when it became more constant and severe; blood was passed at intervals. During the past one and one-half years the patient had lost 10 to 15 pounds in weight and had become weak and dyspneic on exertion. One year before sore-mouth developed, at times severe enough to make eating difficult. During the past one and one-half months numbness and tingling had been noticed in the hands and feet.

Examination. The examination of pus from around the teeth revealed many motile ameba and two organisms from the Flagellata, one evidently Trichomonas, the other narrower and much longer than Trichomonas. The total gastric acidity was 8; free hydrochloric acid 0. In the examination of the stool large numbers of *Balantidium coli* but no ameba were found. The blood picture is shown in Table I.

Treatment. Blaud's pills, Fowler's solution, and rectal injections of vinegar and tannic acid were given. For six months there were marked improvement and gain in weight with a great reduction in the number of *Balantidium coli* in the stools. Reëxamination after nine months showed no *Balantidium coli* in one stool test, but the clinical symptoms and blood picture of pernicious anemia were still present.

Case A185278, Mr. G. A., aged thirty years, a farmer who had never been outside of Illinois, Minnesota, and Iowa came for examination February 9, 1917. The patient's father had died of pernicious anemia one year before. Nine years before and two years before the patient had had short attacks of diarrhea. Five weeks before he had had "grippe" and one week later he had had a sudden attack of pain at the right costal margin running up into the chest

BLOOD FINDINGS IN FOUR PATIENTS HAVING BALANTIDIUM COLI

	A52257		A185278			A215036		A21480			
	4/26/11	1/2/12	2/19/17	3/12/17	9/28/17	11/27/17	12/21/17	5/5/20	5/19/20	8/19/20	9/16/20
Hemoglobin (%)	35	43	35	70	40	44	48	25	39	58	55
Erythrocytes (millions)	1.6	1.97	2.1	3.14	1.66	1.6	2.76	1.97	2.14	2.86	2.84
Color index	1.1	1.0+	0.8+	1.1+	1.2+	1.3+	0.8+	0.6+	0.9+	1.0+	0.9+
Leukocytes	10,400	9,700	11,800	9,400	3,600	4,600	5,900	9,800	6,000	4,400	4,900
Cells counted	300	300	300	300	300	300	300	200	200	200	200
Polynuclear neutrophils	58.6	66.7	66.3	64.3	54.7	55.3	44.3	67.0	39.0	48.5	36.0
Small lymphocytes	32.4	29.0	26.0	29.3	37.7	33.7	45.3	29.0	53.0	41.5	58.0
Large lymphocytes	4.0	1.7	6.3	4.7	4.3	1.7	6.3	4.0	7.0	7.0	3.0
Eosinophils	5.0	1.7	1.3	1.7	2.7	8.7	3.7	....	0.5	2.0	2.0
Basophils	....	1.0	.....	....	0.3	0.7	0.3	....	0.5	1.0	1.0
Neutrophilic myelocytes	....	....	....	....	0.3						
Normoblasts	4.0	1.0	1.0	....	8.0	....	....	....	1.0		
Megaloblasts	8.0										
Poikilocytosis	Marked	Marked	Moderate	Moderate	Marked	Moderate	Marked	Moderate	Moderate	Moderate	Moderate
Granular degeneration of erythrocytes	Slight	....	Moderate	Slight	Marked	Moderate	Moderate	Moderate	Slight	Slight	Slight
Polychromatophilia	Slight	....	Moderate	....	Slight	....	....	....	....	....	Slight

and right shoulder and difficult breathing. Diarrhea had been constant since the attack of grippe, with from four to five loose stools in the early morning and at night.

Examination. The patient was pale and sallow. He had pyorrhea and much bridge-work in his mouth. The systolic blood-pressure was 116, the diastolic 54. The urine was negative for bile and urobilinogen, but urobilin was present. Roentgenograms of the chest and teeth were negative. The blood picture is shown in Table I. The duodenal contents showed a brown trace of bilirubin, urobilinogen 1000 units, and urobilin 1400 units, indicating increased blood destruction. The examination of the central nervous system was negative. Six stool tests showed *Balantidium coli* but no other parasites.

Treatment. Thymol and Blaud's pills by mouth and enemas of kerosene were given; in three weeks this man eliminated almost all of the *Balantidium coli* and raised the hemoglobin from 30 per cent. to 70 per cent. The patient went home feeling much improved.

Examination six months later showed the *Balantidium coli* still in the stools and the clinical picture and blood findings of pernicious anemia. Examination of the central nervous system showed the cord changes usually found in pernicious anemia. The patient was again treated with thymol, salol, Blaud's pills, and Fowler's solution, but he left for home after three weeks, unimproved. He died the following summer.

Case A215036, Mr. G. H. B., aged fifty-two years, a farmer, was examined November 26, 1917. The patient's father, brother, and sister died of similar trouble, "thin blood." For twenty years past the patient had had spells of pain in the upper abdomen lasting for from one to two hours, with vomiting. He had had malaria at the age of fifteen. During the past year diarrhea had been persistent, five to six stools daily. He had lost about 60 pounds in weight; he had lost strength progressively and in the past three months numbness over the entire body with tingling in the extremities had come on. His appetite was poor; he had not had a sore tongue. His memory had failed for two months and recently he had been irritable, and had had crying spells.

Examination. The blood picture may be seen in Table I. The systolic blood-pressure was 150, the diastolic 100; the pulse 84. Examination of the urine was negative. The total gastric acidity was 10, free hydrochloric acid 0. Roentgenograms of the stomach were negative. Two blood Wassermann tests were negative. Proctoscopic examination showed very slight proctitis for 14 inches. The stool test revealed *Balantidium coli* but no other parasite. Examination of the central nervous system showed subacute combined sclerosis.

Treatment. The patient was treated for two months with thymol, chloroform, Blaud's pills, and hydrochloric acid without improvement. The *Balantidium coli* persisted in the stools and the blood picture remained the same. The patient died two months after leaving the Clinic.

Case A21480, Mr. F. L. S., aged fifty-seven years, a farmer, was examined in the Clinic May 4, 1920. One sister had died of anemia at forty-eight. The patient had come to the Clinic eleven years before on account of weakness and loss of strength with spells of diarrhea, at times severe. One stool test had showed occult blood. The protoscopic examination had been negative. During the following years the patient had had spells of diarrhea every ten days, lasting four or five days, with four or five watery stools a day, usually in the morning. Between attacks the stools were normal. Eight months before examination the patient had returned from the state fair with diarrhea and abdominal cramps. He noticed numbness in the extremities, his feet felt "asleep, or as if varnished," and had some weakness of the anal and vesical sphincters.

Examination. The patient's systolic blood-pressure was 116, diastolic blood-pressure 78, pulse 84. The test of the urine and the Wassermann test on the blood were negative. The total gastric acidity was 46, the free hydrochloric acid 0. Foci of infection were not found in the teeth or tonsils.

After tests on the stool and blood were made in the Clinic the patient went away for two days to visit relatives; he was brought back on a cot, with hemoglobin of 25 per cent.

Treatment. The patient was treated with distilled chenopodium and he improved in every way. The number of Balantidia was greatly reduced. The patient was given enemas of vinegar and tannic acid every second day and arsphenamin intravenously once a week for five weeks. After the last treatment nine stool tests, August 5, 6, 12, 13, 19 and 20 and September 16, 17 and 18, failed to show any Balantidia. The clinical symptoms of pernicious anemia are still present and the last blood test, September 16, showed 55 per cent. hemoglobin.

The examination of the central nervous system on three occasions is interesting in showing progressive involvement. May 11, when the hemoglobin was 30 per cent, the neurologist reported slight subacute combined sclerosis, hardly as extensive as in the average case of pernicious anemia of the same severity. July 14 the neurologist reported evidence to be insufficient for a diagnosis of a central nervous system lesion, but findings of combined sclerosis. August 21 the report was subacute combined sclerosis of the pernicious anemia type. This last report was made by a consultant who had not examined the patient previously.

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SOME EXPERIENCES WITH THE MELTZER-LYON METHOD OF DRAINING THE BILIARY SYSTEM.

By Anthony Bassler, M.D., William Henry Luckett, M.D.,

and

J. Raymond Lutz, M.D.,

new york city.

Investigations have been conducted during the past year with clinical cases, operation observations and animal experimentation pertaining to the Meltzer-Lyon method of aspirating duodenal contents after the installation of a solution of magnesium sulphate. This was done for the purpose of proving, if possible, the premises of Meltzer and Lyon as to the accuracy of published statements on the physiological phenomena of gall-bladder function and of this method of treating biliary conditions. We feel that experimental studies on the physiology of influencing motor phenomena of the gastro-intestinal canal or the associated organs in animals cannot be applied, except in a general way, to the physiology of the digestive tract in man. It follows then that clinical and operative experience, when these are obtainable and carefully controlled and deducted from, are more accurate and worth the while, and therefore none of our animal experimentation is presented.

S. J. Meltzer[1] published an article in which he drew attention to the supposed function of the sphincter at the papilla of Vater and

[1] Am. Jour. Med. Sc., 1917, cliii, 469.

the interrelation between the contracting gall-bladder and the sphincteric action at the papilla. He invoked "the law of contrary innervation" to explain the physiological coaptation of contracting musculature and relaxing sphincter. He then suggested testing, by means of the duodenal tube in jaundice and in biliary colic by the local application of a 25 per cent solution of magnesium sulphate, and stated, "It may relax the sphincter of the common duct and permit the ejection of bile, and perhaps even permit the removal of a calculus of moderate size wedged in the duct in front of the papilla of Vater." Lyon[2] adopted this means as a diagnostic test for diseases of the gall-bladder (basing this upon the study of the amount, color, character, cytology and bacteriology of the contents obtained) and advanced the procedure as a means of treating biliary conditions. Since Lyon's articles appeared many have employed this means of diagnosis and treatment, and it now seems timely to present the facts we obtained from a dispassionate study of the method.

Lyon[3] presents five reasons for believing that the darker bile, obtained after a few minutes of aspiration, is obtained from the gall-bladder. These with our experience are offered as follows:

"1. Because I believe that Meltzer's law of contrary innervation as applied to the biliary apparatus is a correct one, and is based upon a sensible interpretation of the most probable mechanism of the physiological storage and discharge of bile." (Lyon.)

Four operative cases were examined with the duodenal tube *in situ*. The abdomens being opened the installation of magnesium sulphate solution was made. None of these were instances of gall-bladder disease. Care was taken not to touch or cause any pressure on the gall-bladder or the ducts. Since vermicular movements of the intestines stop when exposed to air, and they are only active when in contact with the peritoneum, care was taken to keep the upper abdomen closed to air and the normal contact of the parts preserved. At intervals, with as much care as possible, visual examination of the gall-bladder was made, and in no instance was it possible to prove any vermicular action on the part of the gall-bladder or any visible reason to suggest that any contraction took place or that the characteristic dark-colored bile when obtained was from the gall-bladder. For the latter purpose it was sometimes necessary to keep the abdomen open up to one-half hour, which from many aspirations of bile with the method is about the time when the characteristic "*B*" bile could be depended upon to be secured from a single instillation of magnesium sulphate solution.

Independently, one of us (W. H. L.) carried out investigations on operative material to prove or disprove "Meltzer's law of contrary innervation," these being offered in the following cases:

[2] Jour. Am. Med. Assn., 1919, lxxiii, 980–982.
[3] Am. Jour. Med. Sc., 1920, clx, 515.

Case 1.—Appendicitis. The duodenal tube was passed one and three-quarter hours before operation. Right rectus incision. Appendix removed. Upon palpation the tube was found to be in the duodenum, with the tip about opposite the papilla of the common duct. The gall-bladder was palpated and was found full and slightly tense. Fifty cc of a 25 per cent solution of magnesium sulphate were injected into the duodenum. The gall-bladder was gently held in the hand of the operator for eight minutes. It did not contract nor diminish in size. The tension was apparently the same as before injection. Two separate aspirations were now made of the duodenal contents. The gall-bladder was not affected, but was now compressed and easily emptied. Another aspiration obtained very much darker bile than the last specimen.

Case 2.—Appendicitis. The tube was passed one- and one-quarter hours before operation. Right rectus incision. Appendix removed. Upon palpation the duodenal tube was found in the duodenum with the tip about opposite the opening of the common duct. The gall-bladder was palpated and was found apparently normal. Slightly flaccid. Fifty cc of a 25 per cent magnesium sulphate solution were injected through the tube into the duodenum. The gall-bladder was gently grasped and held for five minutes in the hand of the operator. It did not contract. Two aspirations were now made. The gall-bladder did not change apparently. The gall-bladder was now gently compressed, easily emptied and much darker fluid was obtained upon aspiration.

Not being satisfied with palpating the gall-bladder, I determined to try out the test on the first clean case of cholelithiasis, where we could actually visualize the actions of the gall-bladder.

Case 3.—Cholelithiasis. The tube was swallowed one- and one-quarter hours previous to the operation. The gall-bladder was exposed through the right rectus incision. The tip of the duodenal tube was found in the pyloric portion of the stomach by the operator and passed through into the duodenum, extreme care being taken not to touch the gall-bladder. That I had stones to deal with I was sure, as determined by roentgen-ray findings, and upon exposing the gall-bladder the stones were plainly visible. Fortunately, the patient was a thin little woman with a concave abdomen, so that I could observe the gall-bladder without having to wall off any loops of intestines by foreign material, as lap pads, etc. The edges of the wound were gently retracted and lifted upward, and I was enabled to observe the gall-bladder without manipulation and without in any way interfering with its physiology. The question having arisen as to how much the manipulations in the previous tests did interfere with the natural action of the gall-bladder, we demonstrated in this case the peristaltic wave going through several

exposed loops of intestine that were visible to all present. The gall-bladder was sliding up and down with the liver in as natural a condition as possible under the circumstances. Fifty cc of a 25 per cent magnesium sulphate solution were injected into the duodenum and the gall-bladder was directly observed for five minutes. It did not decrease in size, no change apparently taking place. It was the opinion of some of the observers that it had slightly increased in size. First aspiration, light fluid; second aspiration, darker; third aspiration, the same. The gall-bladder was then palpated, compressed and was found to contain numerous stones. The fourth aspiration after compression obtained darker bile-stained fluid.

Case 4.—Appendicitis. Tube swallowed one and a half hours before operation. Right rectus incision. Appendix removed. Stomach palpated. Tube found not to be in the duodenum, but coiled in the stomach with the loop passing across the pyloric end and tip at the cardiac end of the stomach. The tube was passed into the duodenum by manipulation of the operator. The gall-bladder was palpated and was found quite tense and hard. Fifty cc of a magnesium sulphate solution were injected and the gall-bladder held in the hand for eight minutes. It underwent no observable change. Two aspirations—one light and one dark. The gall-bladder was then compressed and emptied, requiring considerable pressure. At the third aspiration much darker fluid was obtained.

Case 5.—Exploratory laparotomy for definite pains in the upper right hypochondriac. Roentgen-ray findings were negative. The patient never complained of pains in or about the appendix. A duodenal tube was passed one hour and thirty-five minutes before the operation. Right rectus incision. A tightly contracted pylorus was observed; the bulb of the duodenal tube was at but not through the pylorus. The gall-bladder was normal. The appendix was a white fibrous rod and was removed. Upon section no lumen was disclosed.

Diagnosis. Fibroid obliterating appendicitis, causing pylorospasm. Pylorus was with difficulty dilated large enough to admit a finger. Invaginated through the anterior gastric wall. A duodenal tube was passed through into the duodenum by the operator. Sixty cc of a magnesium sulphate solution were injected into the duodenum and the gall-bladder was observed, as in Case 3 by direct vision, for fifteen minutes. Absolutely no visible change took place during this time. Two aspirations—light and dark fluid. The third aspiration, after compressing and emptying the gall-bladder, was slightly darker.

In two of these cases the duodenal tube was found by the operator not to be in the duodenum, although distinctly bile-stained fluid was escaping from the outer end of the tube before anesthesia was

commenced. It was suggested that perhaps the tip had been in the duodenum and was afterward regurgitated into the stomach. In the last case, however, although bile was escaping from the tube, the bulb had stopped at the pylorus and we do not think that it was possible for it to have passed through the pylorus at all on account of the pylorospasm present, nor can I account for the bile getting through the same pylorospasm into the stomach.

Case 6.—Appendicitis. Tube swallowed one and a half hours before operation. Right rectus incision. Appendix removed. The gall-bladder and the duodenum were palpated. Tube was found in the duodenum. The gall-bladder was of moderate tension. Fifty cc of a 25 per cent solution of magnesium sulphate were injected. The gall-bladder was held for eight minutes. Four aspirations of duodenal contents were obtained—from clear to dark. The gall-bladder after the last aspiration was thought to have become less tense. The gall-bladder was compressed, easily emptied and much darker fluid obtained on the fifth aspiration. (W. H. L.)

It is a well-known fact that with the identical technic in the same individual, various findings as to different colored bile are obtained at different times. If a relaxation of the muscle of Odii could be obtained at one time with corresponding contraction of the gall-bladder there is no reason that it should not be accomplished at all times that the procedure is practised. The evidence is daily, and always in the same individual even, that the error is beyond what variability of physiological phenomena could account for. It is far more logical to believe that Lyon was overenthusiastic in his acceptance of Meltzer's suggestion as a proved fact. Also, Lyon draws his simile in the action of the gall-bladder with the urinary bladder. It must be remembered that the control in the urinary bladder is entirely voluntary, while that in the gall-bladder is involuntary.

It is a well-known fact that cholectomized pigeons die in a few days from acute pancreatitis, due to the entrance of bile into the pancreatic substance. This danger exists only to a very limited degree in the human, as is proved in acute obstruction of the common bile duct (stone impacted in the common duct). There is a protective equation in bile not being able to gain the general circulation and also in its intense concentration in the biliary channels. In these instances marked distention of the gall-bladder and ducts is met with. It is our belief that in the interval of active bile secretion the pressure within the biliary channels is not as great as during active secretion. We are rather of the belief that the gall-bladder acts as a buffer or pressure-valve to relieve acute distention and protect the pancreatic tissue rather than that its primary function is that of a reservoir of bile for intestinal digestion. This belief is also fortified in that while the human may live without a gall-bladder, Nature dilates the ducts after its removal to compensate for this function of the

channel system, and until this takes place bile flows more steadily into the duodenum. We therefore believe that there is no evidence to substantiate the belief that installation of a 25 or a 33 per cent. solution of magnesium sulphate into the duodenum causes relaxation of the Odii sphincter or that any contraction of the gall-bladder or emptying (even partially) takes place, and therefore the assumption of Meltzer's and Lyon's reasoning seems to be vitiated.

"2. My second reason lies in the fact that the color and viscosity of this second bile indicates a higher concentration, and strongly suggests it as coming from its storage chamber within the gall-bladder." This is further fortified by the observation that bile is found thick and sometimes tarry in diseased gall-bladders containing mucopurulent flakes, pus cells, inflammatory debris, bacteria, etc., and that such are also met with in "*B*" bile. (Lyon.)

This is a very difficult matter to prove in "*B*" biles, the specific gravity of which is so changed (elevated) by the magnesium sulphate content that specific-gravity estimations are quite worthless. We believe that the specific-gravity practically corresponds to the salt content present in the specimen, and, further, that in gall-bladder biles not obtained by this method the specific gravity is not much elevated from hepatic bile, at least to no practical degree by the addition of the mucin it gets in the gall-bladder. This seems difficult to believe, but it is, nevertheless, true. More than that, it is not possible to differentiate mucopurulent flakes, pus cells and inflammatory debris, particularly bacteria, as to what part of the biliary tract they come. They are commonly as largely met with in the first bile (*A*) and not uncommonly in *C* and *D*. When we assume that such findings are from the gall-bladder when there is so much liability of admixture from the duodenum or stomach contents which have been poured into the duodenum, and there is no positive proof in the examination of specimens to sustain it, the liability of clinical error is too great for this statement to go unchallenged. Mucopurulent flakes are far more often from the duodenal mucosa than from the biliary tract, and the same is true of bacteria. On the other hand it is not uncommon that the bile stream at the end of the test (bottle *C* and *D*), "liver drippings," has a larger bacterial content than that obtained in the *B* bottle. The bacteria here are probably from infections of the ducts and perhaps even of the liver substance itself. From these cytological findings we feel that reasoning No. 2 is too liable to error to be conclusive in any way. More than that, the color change to the "*B*" bile is so irregular, often so illy defined and so slowly transitional, that it is not possible clinically to draw definite deductions that the "characteristic bile in bottle *B*" is from the gall-bladder.

It is evidently assumed by the advocates of this method of diagnosis and treatment that the old physiological belief—namely,

that the gall-bladder is a reservoir containing a ready-at-hand supply of bile for quick ejection into the duodenum for the initiation of intestinal digestion—must be true, although it never has been proved and still remains an assumption from anatomy. On the entrance of food into the duodenum it takes but a very few minutes for bile to start running; in fact, it begins running actively when food is still in the stomach. This is accomplished so quickly on the ingestion of food that it is believed by us to occur sooner than a harmonic action from the duodenal mucosa could bring about. If it is due to secretin the secretin must come from the stomach, because it occurs before resorption and stimulation of the hepatic and pancreatic functions could take place after the first entrance of food into the duodenum. It may, on the other hand, be due to some reflex action because it occurs within a few moments after food is in the stomach and promptly when many substances are instilled into the duodenum.

Finally, it is agreed upon by all that the bile contained in the gall-bladder is deeper in color than that which flows directly from the liver substance, and it is assumed by many that this change in color is due to concentration, although the specific gravity estimations do not sustain it distinctly. It more probably is due to oxidation of the biliary coloring matter, the oxygen being derived from the epithelium of the gall-bladder, or, as seems more probable, the first bile secreted by the liver in the process of active digestion contains a large content of oxydase (which is a heavy content in liver substance, particularly in the first bile after a meal). Such a bile then could and would be darker in color without having resided in the gall-bladder. This finding is confirmed in the cholectomized individuals, which cases commonly show characteristic "*B*" bile shortly after operation (one to three weeks) before there has been time for the ducts to dilate, as well as in those cases which have been cholectomized some time before and in whom perfect "*B*" biles are obtained, even if Lyon states to the contrary. From our observations and experiments, then, it is suggested to us that the change of color is due to an oxidation process in which ferments or constituents contained in the bile cause the conversion of color, this dark bile coming directly from the liver substance as well as being caused by residence in the ducts or gall-bladder when ordinary bile low in oxydase naturally would deepen in color.*

"3. My third reason for believing that this second bile is derived largely from the gall-bladder lies in the fact that unless we account

* Dunn and Connell: Jour. Am. Med. Assn., October 1, 1921, present conclusive evidence in a case of hepatoduodenostomy which was carefully studied by them, that the *A. B. C.* bile sequence can be obtained in the absence of the gall-bladder and the common ducts; that these sequences can be repeatedly observed by successive instillations of magnesium sulphate solutions and that the various colored biles are secreted directly by the liver by magnesium sulphate carried to the liver by the portal circulation. These observations confirm those made by us, our article being submitted for publication in June, 1921, and the experimental work was carried out through the winter of 1920 and 1921.

for it as gall-bladder bile we must account for the presence of from one to (in certain cases) nearly six ounces of this darker colored and more concentrated bile as coming from somewhere between the common duct sphincter and the secreting cells of the liver." (Lyon.)

This is partially answered in the above in the quick response of bile secretion on the injection of food into the stomach and its ready flow when anything like food is sent into the duodenum. The above reasoning presupposes that when food is present in the duodenum only such bile as has been formed and is residential in the gall-bladder and ducts is available for use. Einhorn[4] shows that various inorganic salt (sodium sulphate, sodium phosphate, magnesium citrate) solutions stimulate a quick response of bile secretion into the duodenum. Stepp recommended that Witte's peptone in 5 per cent. solution be used for the same purpose for which Lyon uses the magnesium sulphate. Our experience with fibrinated and defibrinated pig's blood, with or without biliary salts, or a solution of biliary salts, accomplished the same thing in the way of a quick secretion of bile with the characteristic color changes that Lyon describes with the magnesium sulphate solution. With the use of any of a number of substances the characteristic *A*, *B* and *C* biles, and mainly the so-called "*B*" bile, is obtained quite as readily as with the solution of magnesium sulphate. There is therefore no specific point in the use of the magnesium sulphate solution when so many other substances accomplish the same end. Our experience has been that if there is any point in obtaining a large quantity of bile in an aspiration there is no better stimulant than a weak solution of hydrochloric acid corresponding to the affinity of gastric juice. Instillation of 50 cc at a time, or 10 cc quantities (which will not give the characteristic changes until three or four instillations have been made), will produce a far larger quantity of bile than any other method. We have obtained as much as 620 cc of bile fluid return after the use of a $\frac{1}{2}$ per cent solution of hydrochloric acid, which in acid affinity corresponds to about one-third the acidity of normal gastric juice.[5] In not a few instances where we have not been able to get the characteristic "*B*" bile we have used hydrochloric acid solution instead of magnesium sulphate, and obtained it far more readily. In fact our experience lately has been that for uniformly obtaining the characteristic "*B*" bile the instillation of from 5 to 50 cc of a $\frac{1}{2}$ per cent solution of hydrochloric acid is a far better procedure than the use of the magnesium sulphate solution. These facts therefore refute the specific action of magnesium sulphate relaxing the sphincter at the papilla of Vater

[4] New York Med. Jour., February 19, 1921.

[5] It has been our experience that the amount and rapidity of secretion of bile correspond to the concentration of hydrochloric acid. However, in using concentrations over 0.5 per cent of the C. P. (31.9 per cent) hydrochloric acid, patients often complain of burning sensations in the epigastrium and "cramps." On the other hand, no ill effects accompany the use of the 0.5 per cent solution, even using quantities up to 100 cc and higher, which give very satisfactory results, as described above.

or influencing favorably the innervation of the gall-bladder, because it stands as irrefutable reasoning that if any one of a number of substances produces the same result as quickly and sometimes more abundantly than magnesium sulphate, Lyon's third reasoning fails to be convincing. It disproves the belief of Lyon that "six ounces" as a large quantity must come from the biliary channel as erroneous. If, on the instillation of magnesium sulphate, six ounces of bile, including the characteristic "*B*" bile, rushed suddenly into the duodenum there might then be some reason to it, but with the magnesium sulphate the flow is slow and the characteristic "*B*" bile does not occur until some minutes, often as long as thirty. In the same individual the characteristic "*B*" bile may be obtained much quicker with the use of a weak solution of hydrochloric acid, and perhaps in varying lengths of time with solutions of other characters. It is true that with the instillation of a weak solution of hydrochloric acid the specific gravity is low, and no doubt there is a considerable content of succus entericus; but, nevertheless, as judged from the color of the material obtained, larger quantity than six ounces is secured directly from the biliary channel. We therefore believe that if the obtaining of bile in quantities is an important point in a therapeutic way, and this bile possesses all the characteristics of that obtained from an instillation of magnesium sulphate solution, the use of a weak solution of hydrochloric acid is a far better means to obtain a large quantity than magnesium sulphate.

"4. My fourth reason, and I feel it is the strongest, for believing that this second type of darker yellow and more viscid bile is actually coming in large part from the gall-bladder, lies in this (I think) convincing fact—namely, that in the cholecystectomized patients that I have studied postoperatively, some ten or more cases, I find (*a*) that I never recover the second type of dark bile but pass immediately from the light golden yellow or relatively more concentrated common-duct bile to the light lemon yellow and limpid bile that I believe is freshly secreted liver bile and collectable for long periods as rapidly as it is secreted, and (*b*) I find that (in this cholecystectomized group) in the larger number of instances, bile is continuously entering the duodenum in the fasting stomach and duodenal state, indicating that the duct sphincter is in a state of inhibited tonus, probably permanently so, since the antagonistic or contrary innervation has been cut when the gall-bladder was removed." (Lyon)

This has already been answered. Characteristic "*B*" biles are are not only obtained from the vast majority of cholectomized individuals but also from those not yet out of bed from the operation before the ducts have had a chance to dilate to take up a gall-bladder function. It is true that in an occasional one the characteristic "*B*" bile is not obtained with the magnesium sulphate solution, whereas it might readily be with a weak solution of hydrochloric acid or other stimulant, and as one has experience through

many people without gall-bladders, here and there, one is met with in which it is not obtained with any stimulant. But this is not proof that "*B*" bile is from the gall-bladder because there is practically as large a portion of people having gall-bladders in which no stimulant causes the "*B*" bile to occur. If one studies this method in true achylia gastrica cases (atrophic gastritis) it will be found that magnesium sulphate solution but rarely secures a "B" bile, while with the weak hydrochloric acid solution it can often be obtained. It is true that in cholectomized individuals the flow of bile is seemingly more steady into the duodenum, but the "*B*" bile is present just the same, and in many the whole phenomenon from the instillations is quite as in normal individuals. This reason does not hold true to our clinical experience.

"5. I might add a fifth reason, to the effect that in my post-operative group of cholecystectomized patients upon whom this non-surgical method has been practised (because the length of time over which surgical drainage could be maintained has not been sufficient to allay the catarrhal inflammation or to arrest the infection), that is in this group, together with a group of non-operated patients with cholecystitis or with gall-bladder biliary stasis, I have seen this second-type bile, easily demonstrable as pathological, gradually clear up and return to a more normal appearance under biweekly drainage by this method." (Lyon.)

This, it occurs to us, is entirely a happy assumption and will remain so until it is proved that the so-called "*B*" bile is derived from the gall-bladder, which in our belief has not been done. It has not been proved on observations with the abdomen opened, and Crohn, Reiss and Radin,[6] in a recent article, experimenting upon dogs in which he (R.) injected a small quantity of methylene blue in physiological salt solution into the gall-bladder and watching the flow of bile from the papilla into the duodenum, noticed that the flow of bile was almost continuous after a meal, and that this bile consisted entirely of liver bile, the blue discolored gall-bladder bile not appearing at all except when manually expressed. More than that, we have taken quite a few definite cases of gall-bladder pathology and have seen no lasting improvement. There are many who do fairly well, but our belief today is that the less the pathology the more the benefit. Apparently there is benefit to be obtained in the simple catarrhal conditions mainly when this is in the ducts (cholangitis). No benefit can be obtained by the method alone in cholelithiasis, with or without biliary colic, and especially in the latter, excepting such as comes from moral effect on the patient of seeing dark bile being aspirated and assuming that it must do some good. There is often a symptomatic benefit in the true gall-bladder case, but it is difficult to decide that this is actual because these cases often have distinct remissions of

[6] Jour. Am. Med. Assn., 1921. (Not published when this Ms. was submitted.)

symptoms and feel quite well without any treatment. Our purpose here is not to dilate on this part of the subject, because we have had enough material and experience to present this more fully later on. We desire only to draw attention to the fact in *bona fide* pathology of the gall-bladder that the method has no comparison in results with proper surgery.

Pharmacology has taught us that in the ingestion of salines, mainly those of a purgative nature, these are not resorbed into the portal stream and excreted by the liver. Our experience has refuted this in the sense that in all biles obtained by the magnesium sulphate method, magnesium sulphate is present in the bile. This content of magnesium sulphate continues up to two hours and more. It was our belief at one time that the magnesium sulphate content was probably derived from the duodenum either by the magnesium sulphate solution being residual in the duodenum or regurgitated back into the first part. The physiology of the duodenum proves distinctly that anything that enters into it is rapidly discharged into the jejunum. Regurgitation from the jejunum into the duodenum does not take place except in the instance of distal stenosis, interfering with the onward flow of intestinal content into the small intestine. More than this is the fact that in the instillation of a weak solution of hydrochloric acid such returns as are obtained show the presence of hydrochloric acid for only a few minutes after its instillation. The same is probably true of any substance of a fluid nature that is injected into the duodenum.

Smithies[7] states: "Gall-bladder bile fractions of more than 100 cc with specific gravity higher than 1020 are abnormal. They indicate bile stasis." Our belief is that the specific gravity estimation of the aspired bile by this method either in the way of proving that "*B*" bile is from the gall-bladder or for any diagnostic reason is open to too much fallacy to be practically worth the while. We believe that the specific gravity of the various types of bile obtained is due largely if not entirely to the magnesium sulphate content of the bile that comes from the liver.

Fig. 1 shows the various content of magnesium sulphate in *A*, *B* and *C* bile. It will be noted in the right-hand figure of the "*B*" bile that the magnesium sulphate is distinctly more than in *A* or *C* bile. It is our claim that this increment of inorganic salts markedly increases the specific gravity of the specimens obtained. The presumption of higher specific gravity having practical significance cannot be sustained in fact.

The left-hand tubes *A*, *B* and *C* in Fig. 1 are a test using barium chloride, and were found by us to be erroneous. The right-hand figures of *A*, *B* and *C* represent a simple test for comparing the quantities of magnesium sulphate in aspirated bile specimens. It was made as follows: To 2 cc of the specimen were added 2 cc each of a 10 per

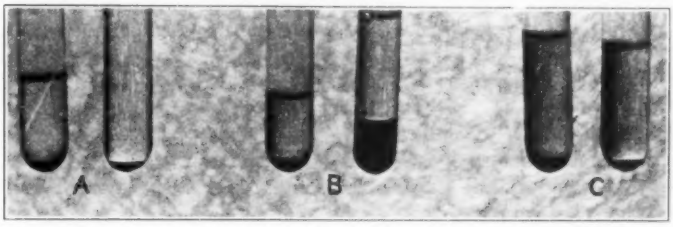
[7] Illinois Med. Jour., April, 1921.

cent ammonium chloride solution, concentrated ammonium hydroxide and 10 per cent sodium phosphate solution. A white crystalline precipitate of magnesium-ammonium-phosphate settles out. This is shown by the chemical equation:

$$MgSO_4 + 2NH_4Cl + NH_4OH + Na_2HPO_4 = MgNH_4PO_4 + 2NaCl + (NH_4)_2SO_4 + H_2O.$$

The amount of the reagents indicated are usually sufficient to precipitate all the magnesium in the 2 cc of the specimen. After the precipitate has settled a little a few drops of the reagent are added. If more precipitate forms the precipitation is not complete and more reagent is necessary. The tubes are then allowed to stand overnight and the sediments compared the following morning. The amount of precipitate formed and the specific gravity have consistently been directly proportional. Since the tests were tried we have found that a more accurate comparison may be made by using graduated centrifuge tubes and centrifuging for two minutes at 1500 revolutions. One cc of a 25 per cent magnesium sulphate

FIG. 1



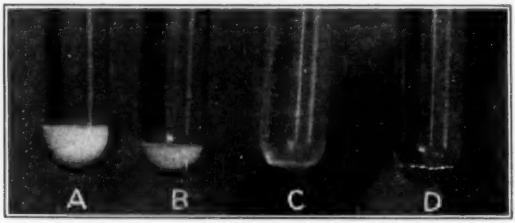
30 c c	60 c c	25 c c
Colorless	Pea-green	Yellow-green
Sp. gr. 1.005	Sp. gr. 1.027	1.004

solution gives approximately 0.5 cc of precipitate. In this way the amount of precipitate and concentration of magnesium sulphate in a given specimen may be roughly gauged. Two cc of the specimen to be examined is a convenient amount to work with. A mixture of equal parts of ammonium chloride and 10 per cent sodium phosphate solutions are added to the 10 cc mark and concentrated ammonium hydroxide solution added to the 14 cc mark. This amount of reagent has been found sufficient to completely precipitate the magnesium in 2 cc of a 25 per cent magnesium sulphate solution.

Fig. 2 shows a graduation in specific gravity according to the content of magnesium sulphate. This observation was made on the same case as Fig. 1 above, and shows the variability in this method, which is one of the most prominent factors of it. Here for some reason we have a large content of magnesium sulphate in the *A* bile and gradually decreasing through *B*, *C* and *D*, having such a slight increase in the specific gravity of the *D* bile that it may be

considered negligible. It may be stated, parenthetically, that the color of the bile is independent of its specific gravity in the presence of magnesium sulphate. Our observation has been that, with the use of the weak solution of hydrochloric acid that we recommend, changes in color correspond more accurately to changes in specific gravity than is true when magnesium sulphate is present in the bile.

FIG. 2



50 cc	30 cc	40 cc	35 cc
Golden-yellow	Pea-green	Light-yellow	Golden-yellow
1.028	1.016	1.010	1.012

As a result of our observations we feel the following conclusions are warranted:

1. The assumption by Meltzer of "the law of contrary innervation" is not proved, and this throws into doubt any specific effect of relaxation of the sphincter of Odii and contraction of the gall-bladder induced by a magnesium sulphate solution.

2. Any one of many substances taken into the stomach or injected into the duodenum will cause a ready flow of bile, of which a solution of hydrochloric acid in about one-third the acidity of normal gastric juice is the most potent for discharge of bile in large quantities and obtaining characteristic "*B*" bile.

3. That the deeper color of "*B*" bile is due to oxidation and not concentration from retention in the gall-bladder, this bile most often coming directly from the liver as a phenomenon of bile secretion.

4. That the viscosity of bile does not elevate its specific gravity to any practical extent.

5. That the margin of error in deducting from the presence of mucopurulent flakes, pus cells, inflammatory debris, bacteria and cells in the aspirated bile as positively coming from the gall-bladder is too great for clinical deduction.

6. That the physiology of the gall-bladder should not be deduced from anatomy and relationship alone—that its most important function seems to be to relieve pressure within the biliary system to protect the pancreas rather than acting as a reservoir for bile in a digestive sense, and that the physiology of bile secretion and gall-bladder function should be studied more thoroughly.

7. That cholectomized individuals show the characteristic "*B*" bile even shortly after operation before the ducts have had a chance to dilate. This occurs so commonly that "*B*" biles cannot always be from the gall-bladder.

8. The increase in specific gravity in aspirated bile by this method is due to the content of magnesium sulphate, which appears to be resorbed into the portal circulation and is excreted by the liver substance in the bile. It is erroneous to deduce clinically in both amount of biles obtained of any gradation (*A*, *B*, *C*, *D*) or by specific gravity estimations as to whether bile stasis exists or not.

9. That where true pathology exists in the gall-bladder the method is a poor substitute for proper surgery. It may be employed in suitable cases as a temporizing means, but it should not be depended upon to correct or definitely benefit pathologically diseased gall-bladders or when gall-stones exist.

ACUTE PANCREATIC NECROSIS.[1]

By John Douglas, M.D.,

ATTENDING SURGEON, BELLEVUE HOSPITAL; ASSOCIATE SURGEON, ST. LUKE'S HOSPITAL, NEW YORK.

It is generally recognized that the cause of acute pancreatic necrosis is related to disease of the biliary system, but just what this relationship is and the various factors which enter into the etiology and pathology of the disease are as yet far from being generally known. Therefore the treatment cannot be based on the soundest surgical principles. It is accepted since the work of Claude Bernard, in 1856, that in animals the injection of certain substances into the pancreatic duct will cause death from or various degrees of the lesion of acute pancreatic necrosis. Bernard used a mixture of bile and olive oil. Since that time these experiments have been repeated, and gastric juice, duodenal contents, solution of acids, alkalies, formalin, bile and bile salts were found to have the same effect, while less irritating substances had little or none.

The work of Opie in 1901, in which he produced acute pancreatic necrosis in animals by the injection of bile into the duct, and his publication of an autopsy finding, in which a small gall-stone obstructed the ampulla of Vater in a patient dying of acute pancreatic necrosis, linked up much of this experimental work with the findings of the disease in human beings. Five years later Flexner proved that the essential constituent of the bile necessary to cause pancreatic necrosis was the bile salts, of which the taurocholate

[1] Read before the Hospital Graduates' Club, New York, March 25, 1920.

was the more active. He also showed that the mixture of mucin, due to its action as a colloid, with the injected material rendered it less active.

Other clinical and experimental observations have been responsible for various theories. It was found that experimental obstruction to the ampulla alone did not cause acute pancreatic necrosis and that small quantities of bile frequently entered the duct without causing any lesion in the pancreas. However, the injection of a bacterial culture into the gall-bladder under the same experimental conditions caused pancreatic necrosis. The observation that after the passage of a gall-stone through the common duct there resulted a dilatation or paralysis of the opening in the papilla was responsible for the theory advanced by Hess, and by Williams and Buck that acute pancreatic necrosis was caused by a damming back of the duodenal contents into the pancreatic duct. It has been shown, however, by experiment that after producing low obstruction of the duodenum it was impossible under normal conditions to force back the duodenal contents into the common or the pancreatic duct. This theory will be further considered later.

There is also the theory, strongly supported by Deaver, on which he has written extensively, of the retrograde infection through the lymphatics from an infection of the gall-bladder. In an article on acute pancreatitis published in 1917, he writes: "The work of Bartels, Arnsperger, Franke, Deaver and Pfeiffer, and Sweet has seemingly established the fact that such extension commonly occurs by way of the lymphatics, which form a rich anastomizing network in the retroperitoneal tissues about the pancreas." He also states that such infection may occur from a duodenal ulcer, appendicular infection or colitis. In an article published in 1919 he repeats this theory, stating: "Inflammation of the gall-bladder is followed by enlargement of the cystic lymph glands, periductal lymphangitis, enlargement of the glands at the head and at the margin of the pancreas and often of the regional lymph channels at the head of the pancreas." While it is true that this lymphadenitis does occur, there must also be considered the facts that infection does not usually occur against the lymph stream, especially after the passage through several chains of lymph nodes; and particularly the fact that the pancreatic lesion is not primarily an infection but a necrosis, with infection not occurring at all, or if it does occur, it is a secondary process. Also, even when an abscess of the pancreas results, it is frequently sterile. Therefore, in view of the known experimental facts, the enlarged peripancreatic lymph nodes may better be explained as secondary to the pancreatitis rather than the etiological factor.

The experimental work of Archibald has done much to explain an important factor in the production of the lesion of acute pancreatic necrosis. By his experiments on cats he found that the

small sphincter at the common duct orifice, first described by Oddie in 1887, furnished this link. Oddie had demonstrated that irritation of the duodenal or even the stomach mucosa, either mechanically or with dilute hydrochloric acid or stimulation of the vagus, would cause spasm of the sphincter and that the sphincter in dogs would resist a pressure of 50 mm. of mercury. Archibald, by the introduction of infected bile under just sufficient pressure not to overcome this sphincteric action, was able to cause the death of a cat from acute pancreatic necrosis in twenty minutes.

These experimental observations then would explain the various factors in the etiology of the disease. They have been stated by Archibald as: "First a change in bile composition increasing the proportion of bile salts: second, undue resistance, perhaps often amounting to spasm of the common duct sphincter; and third, abnormal rise of pressure in the biliary system behind, either in the gall-bladder or common duct." The necessity of the presence of all of these factors makes easier to understand several things previously explained with difficulty.

It must also be recognized that the disease is primarily a necrosis caused by the introduction of the changed bile into the duct. The other pathological changes which occur are secondary. Hemorrhage is a result of destruction of the vessel walls in the gland, due probably to the cytolytic action of the altered bile with later digestive ferment action. Suppuration is always secondary. Therefore the terms suppurative or hemorrhage pancreatitis or the old term pancreatic apoplexy are misleading and the term pancreatitis, usually used, itself is a misnomer, the primary lesion not being an inflammation, but a necrosis. The factor of the infection of the bile as a cause is primarily due to change of the proportion of bile salts causing necrosis and not to its action as an infective agent. It is also possible that infection precipitates the mucin from the bile, thus removing an element which renders it less destructive. A stone in the cystic duct might have the same effect by preventing the mucin from the gall-bladder mixing with the bile. Herein also lies the explanation of the relative frequency of the presence of gall-stones in cases of acute pancreatic necrosis and also explains the disease when gall-stones are absent, because while infection is an etiological factor in gall-stone formation, cholecystitis frequently exists without cholelithiasis.

The early experiments of Oddie, showing that various forms of irritation of the duodenum or even the gastric mucosa by acids, etc., causes spasm of the sphincter at the ampulla of Vater, explains why hyperacidity, duodenal ulcer or alcoholism and similar conditions causing duodenal irritation, in the presence of the other two required factors, furnishes the remaining element in the etiology of an attack of pancreatic necrosis. It is also well known that the secretion and flow of bile is stimulated by its need in the process

of digestion, and therein lies the third necessary element, an increased pressure, and explains why the acute attack frequently follows a heavy meal.

Variations in these three factors result in lesions of different severity. This was demonstrated by the experiments of Archibald. He was able to produce lesions varying from a necrosis which was fatal in twenty minutes to such small areas of focal necrosis in the pancreas that they were not demonstrable without the aid of microscopic examination and which in some instances were and in others were not accompanied by fat necrosis. Archibald has suggested as a result of his experiments the existence of attacks occurring in general practice, characterized by upper abdominal pain which are due to an undiagnosed moderate degree of pancreatic necrosis which does not proceed to the degree of sequestration, and which may even be accompanied by fat necrosis, but the lesion being aseptic is ultimately replaced by a fibrosis.

Three of my own patients exhibited conditions with a close bearing on this subject. An autopsy on a man who died after I had performed an operation for acute pancreatic necrosis revealed, besides the acute necrosis and hemorrhage for which the operation was performed, several areas in the pancreas of fibrosis, surrounding masses of creamy material which had obviously been the result of a previous attack from which he had recovered. His history showed that this attack had occurred one year earlier and had been diagnosed as a gall-stone attack. Another man developed an acute pancreatic necrosis while in the ward of Bellevue Hospital, convalescing from an operation for a urethral stricture. He refused operation, subsequently developed a large mass in the area of the pancreas, had later an elevation of temperature, a Cammidge reaction, which has since proved to be of less value than it was thought at that time, and had fatty diarrhea. This made the diagnosis of a pancreatic lesion obvious, but while he still persisted in his refusal to allow an operation, in the course of time the mass disappeared, he made a complete recovery and left the hospital free of symptoms. His subsequent history is unknown. In a third patient, a colored woman, the symptoms complained of were all referable to the pelvis, and at operation for a salpingitis which was present I noticed areas of fat necrosis in the omentum. After a salpingectomy an incision over the pancreas showed it very hard and indurated with hemorrhagic and greenish gangrenous appearing areas throughout the body of the organ. She made an uneventful recovery.

The first two cases then demonstrate the possibility of recovery from severe attacks and the third case the possibility of a marked lesion without anything pointing definitely to the fact that the pancreas was involved, as Archibald has demonstrated experimentally the possibility of mild attacks occurring with recovery ensuing.

The pathological lesion in the pancreas appears to be due to the

direct cytolytic effect of the changed bile permeating the gland, and Archibald believes that the ultimate extent of the lesion depends on this primary destruction. It is known that the secretion obtained directly from the pancreas has no digestive power until the ferments have been activated. This may occur pathologically by calcium from the blood or bile, inflammatory exudate, the product of an aseptic necrosis, or as it occurs normally in the intestine, by enterokinase, the duodenal secretion; and the trypsinogen thus activated probably carries on some of the destruction previously originated. It is interesting to note, however, that in gastric resections or operations in which an adherent ulcer or carcinoma of the posterior stomach wall necessitates an injury or even a shaving off of pancreatic tissue, neither protein digestion of neighboring tissue nor fat necrosis occurs.

Even if we accept, however, the experimental and clinical facts which prove that the injection of changed bile into the pancreatic duct causes pancreatic necrosis, and explain the variations of the lesions by the different factors, contributing to the degree of the necrosis, it cannot be recognized as the cause of all cases of pancreatic necrosis. Opie in his book on *Diseases of the Pancreas* quotes various case reports in which the reflux of bile could not have been a factor. In one case reported by Eliot the duct of Santorini was the larger and entered the duodenum about 1.5 cm. above the papilla, through which emptied the smaller duct of Wirsung and the common bile duct. The necrosis in this case was most marked in the portion of the gland drained by the larger duct of Santorini. Johnstone reported 2 cases of pancreatic necrosis in which the pancreatic duct opened into the duodenum 1 or 2 cm. above the common bile duct opening. Basset reports 1 case in which the necrosis involved the area drained by a small duct of Santorini which entered the duodenum through a small diverticulum above the papilla.

The theory that duodenal contents might be forced back into the pancreatic duct and thus cause pancreatic necrosis has been already mention in this article, together with the work of Hess and of Williams and Buck, who observed a paralytic dilatation of the opening of the common duct after the passage of a stone, and assumed that this allowed the reflux of duodenal contents. Archibald writes: "This theory still remains theory." The anatomical conditions reported by Eliot, Bassett and Johnstone demonstrate, however, the impossibility of biliary reflux into the pancreas being the etiological factor in their cases, and as it is known that duodenal contents injected into the duct will cause pancreatic necrosis (Polya), it seems fair to assume that this was the cause of the pancreatic necrosis in the cases mentioned; for while, as has also been previously mentioned "under normal circumstances, it has been found impossible by experiment, such as complete obstruction, to force back the duodenal contents into the common duct," in the cases quoted by

Opie these were not normal circumstances, as the duct in relation to the area of necrosis entered the duodenum by an independent orifice. It is assumed that the reflux from the duodenum is prevented by the sphincter of Oddie. Whether in the presence of an independent opening of the duct of Santorini a sphincter is also present I do not know and can find nothing written on the subject. If there is no sphincter this might explain the occurrence of a pancreatic necrosis due to duodenal reflux along the course of this duct. This is also the only theory which remains to be proved or disproved by anatomical examinations of specimens when this less usual arrangement of the ducts is found.

Fat necrosis is an interesting phenomenon resulting from the pancreatic lesion. Apparently the basement membrane of the acini, as well as the connective tissue binding the lobules of the glands, is sufficiently destroyed to allow the escape of a certain amount of lipase, the fat-splitting ferment, and this attacking the fat in small areas, splits the fat globule into a fatty acid and glycerin, and the fatty acid combining with calcium salts forms an insoluble soap which appears in the omentum, mesentery and subserous fat and on the surface of and about the pancreas as small white opaque spots. In an autopsy on a patient who died after an operation for acute pancreatic necrosis these areas of fat necroses were found extending down retroperitoneally as far as the pelvis. This fact seems to me to have a bearing on the treatment, as I shall mention later. It is easy to understand this direct extension of the pancreatic ferments, but I am unable to discover any adequate explanation of why these small isolated areas of fat necrosis so diagnostic of pancreatic involvement occur at a considerable distance from the gland or how the lipase is carried to these areas. Turner has reported two cases of acute pancreatic necrosis in which he made the observation that one presented an area of discoloration and edema of the skin about the umbilicus, the other a similar condition in both loins, due to subcutaneous fat necrosis by direct extension.

Considered from the foregoing viewpoint of the etiology and pathology of the disease, as being essentially a primary necrosis and not an inflammatory process, its symptomatology is more readily understandable. The primary attack with its extreme pain, excessive prostration, subnormal temperature, shock and vomiting and resemblance to an acute intestinal obstruction, may be understood by the consideration of certain factors. The extreme pain is due to the immediate swelling of the gland and the pressure resulting therefrom. The absence of infection and of consequent irritation of the peritoneum explains the absence of early rigidity so characteristic of a perforation of a stomach or duodenal ulcer or perforated gallbladder from which it is usually necessary to differentiate the acute fulminating attack. The vomiting, shock and extreme prostration, subnormal temperature and absolute constipation which resemble so

clearly the symptoms of an intestinal obstruction, while partly explained by shock or reflex action, is further explained by the biochemical similarity in the toxin produced in both processes. As shown by Whipple, the cause of death in cases of high intestine obstruction is a split-proteid product of the nature of a peptone developed in the mucous membrane of the intestine. It is reasonable to suppose that the pancreatic necrosis followed by the digestive action of the activated trypsinogen results in a similar toxic product. This again is a factor which must be considered in determining treatment. In the acute fulminating cases this is probably the cause of death. Dobrauer has transplanted necrotic pancreatic tissue into the peritoneum of dogs with resultant death. In those cases in which the primary damage to the pancreas is less extensive the similarity to a low intestinal obstruction is more marked. In a patient on whom I recently operated the bowels could not be moved by enemata for forty-eight hours and a mass in the epigastric region suggested a carcinoma in the transverse colon, there being no temperature elevation. The roentgen ray demonstrated, however, that a barium enema easily filled the large intestine, making the diagnosis of pancreatic involvement practically certain.

In view of the foregoing conception of the etiology and pathology of this disease it would appear that we should question the accepted treatment of this lesion. Based on the theory of an acute infection, the treatment of an infection of any part of the body being always drainage and removal of the infection when this is possible, the treatment advocated has been and still is drainage of the pancreas either by gauze, tubes or rubber dam down to or into the organ by cutting the capsule or boring into it by a blunt instrument.

In the discussion of a paper on "The Treatment of Acute Pancreatitis" before a surgical society, in which seven members of the society took part, the discussion being published in the *Annals of Surgery* in 1917, mention of drainage of the biliary ducts or gall-bladder was made in only one case, the discussion being confined to the best manner of drainage of the pancreas itself.

If, however, the lesion in its primary aspect is a necrosis and the cause of death in the acute fulminating cases, poisoning by a split protein product, can this necrosis be drained and does not the injury caused by the attempts at drainage cause more damage to the organ? Also the experiments of Whipple and Goldpasture showed that the exudate about the pancreas had a protective action against the liberated ferments. As to drainage of the gall-bladder or common duct, which would seem to be indicated by the foregoing theory of the etiology and which I have practised in these few cases on which I have operated during the past five years, if Archibald's idea that the amount of the primary lesion is determined by the amount and virulence of the bile entering the duct then the amount of that damage cannot be lessened by biliary drainage, but we do not know

whether or not this reflux of bile may be repeated. Those cases which after a period of improvement suddenly get worse would suggest that this happens unless an elevation of temperature and other signs of infection ensue. I have recently seen a patient operated on for acute pancreatic necrosis by Dr. M. K. Smith in St. Luke's Hospital, New York. A cholecystostomy had been done and the patient was convalescent, up and out of bed on the twenty-first day, when she had a recurrence of symptoms similar to the primary attack. The biliary drainage had ceased, but after reëstablishing the discharge of bile the symptoms cleared up.

It has been suggested by Balfour that cholecystectomy would cure chronic pancreatitis, the gradual dilatation of the common and other bile ducts finally overcoming the action of the sphincter of Oddie, but it would seem that in the meantime the pressure in the ducts would be increased and the danger of reflux greater. One of my patients on whom I had performed a cholecystectomy died from a hemorrhage from the wound following an operation for acute pancreatic necrosis occurring two years later.

The suggestion has also been made that cutting of the sphincter of Oddie through an opening in the duodenum be done to prevent its closure and back-flow into the duct. The objection to this would be the difficulty of doing so in a very sick patient, as it might be very hard to accomplish in the presence of an acutely swollen enlarged pancreas, surrounded with exudate and areas of fat necrosis, and there would also be the possibility of a fistula resulting or stricture occurring later.

It must be recognized that either with or without any operative treatment certain of the acute fulminating cases will die unless some means be discovered of combating the protein poisoning which appears to be the cause of death. Of the milder cases many will recover without operation, and it is difficult to determine the correct course to follow in the presence of an acute case. Those patients who appear most desperately ill in the first twenty-four hours would surely have a poorer chance of recovery if a prolonged anesthetization and operation were superimposed on their primary toxemia, but it is not always possible to rule out an acute inflammatory disease of other origin in the upper abdomen which would positively indicate operation.

That it is impossible to drain a necrotic process until the sloughs have separated has been pointed out, but this does not mean that drainage is not indicated. It is of frequent occurrence that if the patient survives the primary necrosis this is followed by a breaking down of areas in the pancreas with the formation of an abscess or cyst, and frequently there is a sequestration of areas of the pancreas which come away in large sloughs. When an acute process is present and the pancreas has been exposed, either through the gastro-colic or gastro-hepatic omentum, if a superficial incision is made along

its anterior surface, parallel with its long axis, this might relieve some of the tension and direct the discharge of subsequently broken-down material. If there is already a broken-down area this may be opened down to with a blunt instrument. It has been my practice to lead down to this a large gauze pack, protected from the peritoneal contents above and below, as well as the skin, by a rubber dam. This for the purpose of allowing later discharge of broken-down material and protecting as a cofferdam the rest of the cavity. I am opposed to the use of rubber-tube drainage, as usually recommended, for two reasons: First, there is nothing to drain out of the tube in the early cases, and second, because of the tendency of the tube to cause pressure necrosis of neighboring vessels or even the intestine. I have had 2 patients die, 1 after three days and 1 fourteen days, after operation for pancreatic abscess, due to profuse hemorrhage from the wound, evidently from one of the large blood-vessels in the vicinity of the pancreas.

Unless an abscess or broken-down, softened area is present I do not see any special advantage to be gained by following the usually advised method of boring into the gland with a blunt instrument, such as a clamp or scissors, and it seems to me to have very obvious disadvantages, such as damage to tissue which has not already become necrotic and the condition found at the autopsy which I have previously mentioned, in which the fat necrosis had followed the retroperitoneal tissue planes, made me feel that I had been somewhat responsible for this portion of the after-results in my efforts to drain the pancreas.

Finally, in respect to the question of the advisability of biliary drainage, even though it be accepted that the maximum damage is accomplished with the primary reflux of bile, as we do not know whether this reflux may be repeated, it would appear that biliary drainage should be established if its accomplishment would not by prolongation of the operation jeopardize the recovery of the patient. The number of cases in which the unusual termination of the ducts exclude the possibility of biliary reflux as an etiological factor must form too small a group to indicate the omission of this step in the operative procedure, as even in these cases, if rapidly done, it can do no harm. In a case in which no stones are present in the gall-bladder it is usually easy in a few minutes to establish a cholecystostomy through a stab wound in the right hypochondrium, the tube being sutured into the gall-bladder through the primary incision and then led out through the stab wound. Whether in the presence of cholelithiasis, with or without a small contracted gall-bladder, cholecystectomy should be done and the common duct drained would become a matter of judgment, depending on the individual case and condition of the patient for determination.

IMMUNE BODIES IN A TYPE I LOBAR PNEUMONIA.

By Edward Steinfield, M.D.,
PHILADELPHIA.
AND
Herbert J. Darmstadter, M.D.,
PHILADELPHIA.

(From the Medical Service of Edwin A. Heller, M.D., and the Clinical Laboratories of the Jewish Hospital.)

The study of the development of immune bodies in the serum of patients recovering from lobar pneumonia has at all times been of interest because of the close association found by all investigators between the crisis and the appearance of these bodies. Occasionally discordant results had been obtained in such tests by observers who did not use strains of pneumococci homologous with those infecting the patient. In recent years the question has been fully studied particularly by Dochez,[1] Clough[2] and Chickering.[3] Dochez found the serum after the crisis to contain large amounts of protective substances in a study of cases before the biological classification of the pneumococci was recognized. Clough also found ample evidence of immunity in the form of protective bodies and also that the serum taken during recovery was capable of stimulating phagocytosis of homologous pneumococci. The investigations of Chickering were mainly upon cases of Type I pneumonia, some of which had received Type I antiserum. He stated that agglutinins developed just before or just after the crisis and he thought that the use of immune serum had little influence in the development of these bodies. The occurrence of large amounts of agglutinins and protective bodies in a case of Type I pneumonia treated with Type I antiserum has seemed to us interesting enough to record, especially since it is our impression that the clinical improvement and the presence of these immune bodies were related to the administration of the serum.

The patient, C. D., male, aged twenty years, was admitted October 15, 1920, with a temperature of 102° to 103° F., and with atypical pulmonary signs suggesting influenza. In several days consolidation was manifest in the lower lobes of both lungs. The leukocyte count was 24,800. A Type I pneumococcus was found in the sputum. The other laboratory and clinical data of importance were as follows: Urine: specific gravity from 1030 to 1023; a heavy

[1] Jour. Exper. Med., 1912, xvi, 665.
[2] Bull. Johns Hopkins Hospital, 1913, xxiv, 295; Ibid., 1919, xxx, 167.
[3] Jour. Exper. Med., 1914, xx, 599.

cloud of albumin; a number of granular casts. The red blood cells were 3,920,000; hemoglobin, 80 per cent. Blood Wassermann was negative; blood-pressure ranged about 130 systolic and 60 diastolic. Examination of the heart revealed a double aortic lesion and a mitral regurgitation of rheumatic origin and apparently well compensated.

On the sixth day of illness 100 cc of Type I antipneumococcus serum were given intravenously after appropriate desensitization. Eight hours later 50 cc of serum were given. Sufficient improvement was evident by the next morning and no more serum was injected. The temperature fell in a step-like fashion from 101.4° F. to normal in three days after injection of the serum. Six days after the introduction of the serum, serum sickness appeared with a typical urticarial eruption and edema of the face and arms particularly. This was preceded by a marked fall in the specific gravity of the urine to 1005, approximately a day before the onset of symptoms of serum sickness. During the second day of the serum sickness the urine showed 2.11 gm. of total chlorides in twenty-four hours. No particular stress is placed upon these figures since preliminary observations with a standard diet had not been made. However, we were reminded of the studies of Rackemann, Longcope and Peters,[4] who demonstrated a marked retention of chlorides with low chloride output in the urine during serum sickness.

Serum for testing the presence of agglutinins and protective substances was procured from blood removed four days after injection of the immune serum. Agglutinin tests were conducted by the macroscopic method by mixing in small test-tubes 0.5 cc of a twenty-four-hour broth culture of pneumococcus Type I and 0.5 cc of the patient's serum in various dilutions, the final dilution being, of course, double that of the strength of serum used. The test-tubes were then incubated at 37.5° C. for one hour, placed in the refrigerator for twenty to twenty-four hours and read for clumping. By this method the patient's serum showed definite power of agglutination in dilutions up to 1 to 10 (final dilution).

In performing the protective tests it was first necessary to establish a minimal lethal dose. Mice were given intraperitoneal injections of broth cultures in doses ranging from 0.000002 cc to 0.01 cc. All dilutions were made in bouillon to avoid autolysis of the organisms. It was found that the culture was sufficiently virulent to cause death in forty-eight hours, using 0.000002 cc (1 cc of 1 to 500,000) of a twenty-four-hour broth culture.

Mice were then given intraperitoneal injections of various dilutions of the culture, as outlined in the table, together with 0.5 cc of the patient's serum, the dosage being so arranged that the total bulk of fluid did not exceed 1 cc per 20 gm. of weight. Controls

[4] Arch. Int. Med., 1916, xviii, 496.

received 0.5 cc of serum from a normal individual and also culture alone. Observations were made on the basis of ninety-six hours, though, as a matter of fact, those animals surviving this time survived indefinitely. The heart's blood of the dead animals were examined for pneumococci except in those instances in which the body had been mutilated by the survivors.

The results as outlined in tabular form indicate that there were sufficient immune bodies in 0.5 cc of the patient's serum to protect against 500 times a lethal dose of Type I pneumococci. Controls of normal serum did not protect against the lowest dose.

PROTECTIVE VALUE OF PATIENT'S SERUM AGAINST TYPE I PNEUMOCOCCUS CULTURE.

Mouse No.	Culture, c c.	Patient's serum, c c.	Control serum, c c.	Result in days.			
				1	2	3	4
1	0.000002	..	..	S	D		
2	0.000002	..	0.5	S	D		
3	0.00001	..	..	S	D		
4	0.00001	..	0.5	S	D		
5	0.00001	0.5	..	S	S	S	S
6	0.00002	0.5	..	S	S	S	S
7	0.0001	0.5	..	S	S	S	S
8	0.0002	0.5	..	S	S	S	S
9	0.001	0.5	..	S	S	S	S

S = survived D = died.

STUDIES ON THE CHEMISTRY OF THE BODY IN DISEASES OF THE SKIN.

By Oscar L. Levin, M.D.,

ATTENDING PHYSICIAN, DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, BETH ISRAEL HOSPITAL AND DISPENSARY; INSTRUCTOR AND CHIEF OF CLINIC, DEPARTMENT OF DERMATOLOGY AND SYPHILOLOGY, CORNELL UNIVERSITY MEDICAL COLLEGE AND CLINIC; ADJUNCT DEPARTMENT OF DERMATOLOGY, MOUNT SINAI HOSPITAL, NEW YORK CITY

AND

Max Kahn, M.D., Ph.D.,

ATTENDING PHYSICIAN, DISEASES OF METABOLISM, AND DIRECTOR OF LABORATORIES, BETH ISRAEL HOSPITAL; ASSOCIATE IN BIOLOGICAL CHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK CITY.

The changes that may be noted in the blood in conditions of disease of the skin must be viewed very critically before deductions can be drawn that the change in the composition of the blood was due to the pathological state of the skin or that the skin lesion was

the result of the patho-chemistry of the blood. The appreciation of cause and effect is a difficult matter in such studies, for the deviation in the composition of the blood may be due to altogether other factors than the skin pathology and the skin lesion may be not at all the effect of the causative factor of the blood changes, but may be due to some totally different cause.

It may be that a patient suffering from nephritis, for example, may have a coincident eczema. Now, one cannot ascribe the marked disturbances in the blood chemistry to the eczema nor can one state with any shadow of definite evidence that the eczema was due to the blood changes observed. It is therefore necessary to scrutinize results and to be conservative in drawing conclusions in such researches.

We have endeavored in this preliminary attempt to observe if any change is constant in any dermatological affection. In most of the patients we examined the blood for its carbon-dioxide combining power according to the method of Van Slyke; for non-protein nitrogen according to Greenwald's technic; for urea nitrogen according to the urease method of Van Slyke and Cullen; for creatinin by the method of Folin; for glucose according to the method of Lewis and Benedict. In certain cases we also examined the blood for uric acid by the method of Folin and Denis and for cholesterol by the process of Autenrieth and Funk. The accompanying tables record the figures obtained in this series of experiments.

Discussion. Barber and Semon, studying the relation of seborrhea to body chemical changes, classified seborrheic individuals into two groups: (1) Those who have an exudate diathesis and are congenitally predisposed or acquire the tendency in infancy, and (2) those in whom the condition is of sudden onset and give no history of an exudative diathesis. They however remark that both of these types are characterized by an acidosis, as is evidenced by the hyperacidity of the urine and the reaction to treatment by alkalies. They somewhat confuse the subject by comparing the condition to diabetic ketosis, though they point out that there is no resemblance in degree between the two conditions. It seems to us that the acidosis of seborrhea is, if anything, of the true increased hydrogen ion concentration type, whereas the acidosis of diabetes is due to the ketonic substances generated by the improper decomposition of fats due to the maloxidation of carbohydrates. Whereas the true acidosis will clearly be helped by the administration of alkalies, the ketosis of diabetes will not be relieved by that medication. The authors attempted to indicate a similarity in the two conditions of diabetic ketosis and seborrheic acidosis, implying a supposition that the basic disturbance may be similar, whereas the acidosis in seborrhea is, if anything, the underlying cause of the skin condition, the ketosis of diabetes is the resultant of carbohydrate-fat maloxidation. According to the experiments of Barber and Semon the condition

of acidosis has no relation to and should not be contrasted with (in our opinion) diabetic acidosis.

BLOOD CHEMISTRY; MISCELLANEOUS SKIN DISEASES.

No.	Diagnosis.	CO_2	Urea N.	NPN.	Creatinin.	Uric acid.	Glucose.	Cholesterol.
1	Urticaria	52	9	22	1.5			
2	Urticaria	..	12	34	....	....	0.12	
3	Urticaria	48	28	38	2.8	....	0.09	
4	Angioneurotic edema	48	18	26	2.1	4.2	0.14	147
5	Purpura	36	26	38	2.6	2.5		
6	Purpura	56	9	..	....	....	0.11	
7	Erythema	58	17	30	1.2	....	0.56	
8	Erythema	40	10	16	0.7	....	0.11	
9	Erythema	46	11	24	2.0			
10	Erythema multiforme	30	12	25	....	....	0.13	
11	Erythema multiforme	59	13	20	1.47	....	0.12	
12	Erythema nodosum	54	9	26	1.2			
13	Dermatitis herpetiformis	50						
14	Gangrene	..	....	..	....	....	0.17	
15	Gangrene	..	....	..	....	....	0.18	
16	Gangrene	30	9	..	....	....	0.24	
17	Gangrene	..	....	..	....	....	0.16	
18	Perforating ulcer	..	....	..	....	....	0.19	
19	Thrombo-angeitis obliterans	42	24	35	2.3	4.75	0.18	
20	Rosacea	52	10	26	0.8	....	0.09	
21	Lupus erythematosus	76	10	38	1.0			
22	Scleroderma	62	18	25	1.8	....	0.165	
23	Scleroderma	42	11	24	3.4	3.2	0.09	167
24	Pruritus	64	....	..	....	....	0.078	
25	Folliculitis	46	21	27	....	....	0.18	
26	Carbuncle	36	....	..	....	....	0.36*	
27	Carbuncle	28	12	23	2.0	....	0.32	
28	Carbuncle	..	....	..	....	....	0.1	
29	Gumma (lues)	46	19	37	2.4	....	0.11	
30	Lichen planus	48	13	30	0.6			
31	Pompholyx	64	10	21	1.7	....	0.1	
32	Xanthoma	..	....	..	....	....	0.13	210
33	Erythema	58	16.5	21	2.8	....	0.11	
34	Chloasma	50	12	23	....	....	0.09	
35	Hyperidrosis	52	17	24	1.9	....	0.95	
36	von Recklinghausen's disease	60	8.3	36	1.2	....	0.07	
37	Pityriasis rubra pilaris	74	....	..	....	....	0.07	
38	Hodgkin's disease	60	8	12	1.9	....	0.22	
39	Moeller's glossitis	63	12	23	1.5			

Schwartz, Levin and Mahnken studied the carbon-dioxide combining power of the blood plasma in 139 cases of skin lesions. They concluded that a lowering of the alkali reserve of the blood has been

found sufficiently frequently in acne, psoriasis, urticaria, furunculosis and eczema—particularly seborrheic eczema—to warrant further investigation.

We have examined the state of acidosis in a large number of eczema and other skin diseased patients and we shall discuss our results under several headings.

Eczema. The acidosis in this condition was investigated by several methods, although not all of the methods were applied to all the cases. A certain number of patients were examined by all the methods. The urine was examined for total acidity by the Folin method; the formalin titration coefficient was determined by the method of Henriques-Sorensen; the blood was examined for its carbon-dioxide combining power by the method of Van Slyke and the alveolar carbon-dioxide was determined by the method of Fridreicia. The results in 17 cases of eczema thus investigated were as follows:

ACIDOSIS STATE IN ECZEMA.

No.		Total acid urine 24 hours.	HCHO coefficient.	CO_2 blood.	CO_2 alveolar air.
1		514	0.54	62	
2		570	0.55	58	
3		620	0.72	52	
4		600	0.84	56	5.2
5		610	0.93	56	
6		595	0.73	..	5.6
7		480	0.56		
8		570	0.48	..	5.5
9		630	0.92	64	
10		722	1.75	..	6.2
11		882	0.87	58	5.9
12		665	0.75	55	5.8
13		549	0.63		
14	Diabetes	755	1.42	42	4.4
15	"	828	1.98	38	4.2
16	"	970	2.08	36	4.0
17	"	850	2.27	40	

In all 42 cases of mild eczema have been studied. Of these, 4 were diabetics, 1 had furunculosis and 1 had Hodgkin's disease. Acidosis was present in these cases. Of the others only 4 showed a mild degree of acidosis as measured by the carbon-dioxide combining power of the blood. These were Cases 11, 17, 19 and 25. The total acid of the urine, the amino-acid as measured by the formol titration method and the alveolar carbon-dioxide were absolutely normal in those patients in whom investigations were made.

So far as the blood chemistry of patients suffering from mild eczema was concerned nothing unusual was discovered. Of course, in the patients with diabetes the abnormalities that were found were due to the underlying metabolic derangement and were not reported here because they have no concern with the subject under discussion. The figures for urea nitrogen, non-protein nitrogen, creatinin and glucose as well as for cholesterol and uric acid (in

those instances in which they were determined) were altogether normal.

CHEMISTRY OF THE BLOOD IN ECZEMA.

No.	Co_2	Urea N.	NPN.	Creatinin.	Uric acid.	Glucose.	Cholesterol.
1	60	10	22	0.85	...	0.1	
2	57	17	21	1.0			
3	52	11	26	0.6	...	0.09	
4	54	11	20	1.1	...	0.075	
5	..	10	35	....	...	0.09	
6	62	10	26	1.7	...	0.085	
7	58	10	25	1.0	...	0.07	
8	58	20	28	1.8	3.8	0.09	
9	42	14	30	1.2	...		
10[1]	36	....	..	....	...	0.14	
11	50						
12[2]	40	....	..	....	...	0.11	
13	61	18	22	1.5			
14	62	20	30	2.2	...	0.1	
15	58	17	27	2.0	...	0.09	
16	..	9	28	1.4	...	0.074	
17	48	17	..	1.1	...	0.13	
18	52	15	..	1.0	...	0.08	
19	45						
20	58	16.5	21	2.8	...	0.11	
21	52	17	28	2.6	....	0.18	
22	58	14	28	1.6			
23	..	17	27	2.6	...	0.14	
24	28	26	39	2.8	4.1	0.11	197
25	46	9	19	1.2	...	0.08	
26	50	13	28	2.2	...	0.09	

In instances of diffuse eczema in which the sulphur partition was made on the urine we found a marked increase in the ethereal sulphate fractions, seeming to point to some state of intestinal putrefaction. In these cases there seemed to exist a mild degree of acidosis as evidenced by the various tests. The blood chemistry, in general, however, was apparently normal.

Case.	Total S.	Inorganic SO_4%S.	Eth. SO_4S.	Neutral S.%S.
1	1.25	62.5	29.2	8.3
2	0.94	56.8	32.8	10.4
3	0.92	63.4	26.9	9.7
4	0.86	65.7	26.5	7.8

Case.	CO_2 per cent.	Urea N. mg.	NPN. mg.	Creatinin. mg.	Glucose. per cent.	Uric acid, mg.	Cholesterin, mg.
1	42	14	20	2.2	0.09	3.2	152
2	40	17	25	2.4	0.09	2.7	147
3	52	12	27	1.8	0.11	2.8	140
4	55	16	25	2.0	0.08	3.4	159

Case.	Urine acidity.	Amino-acid.	CO_2 alveolar air.
1	620	1.8	4.7
2	790	2.2	4.4
3	680	1.85	5.0
4	785	2.35	4.9

[1] and furunculosis. [2] and Hodgkin's disease.

The sulphur metabolism studies previously reported are those by Géber and by Hammerli in psoriasis, by Stuve in pemphigus vegetans and by Rosenbloom and Cameron in urticaria. Géber's results of an increased excretion of sulphur in psoriasis were not corroborated by Hammerli. Stuve found the sulphur metabolism normal in pemphigus and Rosenbloom and Cameron found but slight variations from the normal in their metabolic investigations in a case of chronic urticaria.

We have found no increase in the non-protein sulphur of the blood in eczema.

The calcium content of the blood was determined in several cases of eczema, but normal figures were obtained.[1]

Acne Vulgaris. It has been reported by Schwartz, Heimann and Mahnken that there is an increase in blood sugar in cases of acne. In 15 cases of acne vulgaris that we have examined 6 gave figures of blood sugar above 0.1 per cent. All the others showed normal blood-sugar content. In 4 cases not necessarily associated with the high glycemia there was reduced carbon-dioxide absorption power of the blood plasma. In general the blood chemistry showed no marked deviation. The non-protein sulphur content was normal.

CaO IN BLOOD IN ACNE VULGARIS.

Case.	Mg. CaO in 100 c c.
1	8.5
2	9.0
3	9.7
4	11.2
5	8.7
6	8.5
7	7.4

NORMAL FIGURES.

Carbon-dioxide combining power of the blood	60	per cent.
Urea nitrogen	16	mgm. per 100 c c blood
Non-protein nitrogen	25	mgm.
Creatinin	1	mgm.
Uric acid	2.5	mgm.
Cholesterol	140	mgm.
Glucose	0.1	per cent.
Calcium oxide	10	mgm.
Carbon-dioxide alveolar air (Fridericia)	6	per cent.
Total acid urine	600	
Formol coefficient	0.75	
Inorganic sulphate sulphur (urine), per cent of total sulphur	70	per cent.
Ethereal sulphate sulphur, per cent of total sulphur	15	"
Neutral sulphur, per cent of total sulphur	15	"

The calcium content of the blood in acne deserves special discussion. Thro and Ehn have recently reported that in acne vulgaris

[1] In a more detailed article complete description of methods and results obtained will be given.

the calcium content of the blood (in 12 cases) showed a marked increase, the figures they obtained being from 13.6 to 25.7 mgm. per 100 cc of blood. They attempt to deduce some relationship between the condition of acne and this calcium increase in the blood. In cases of furunculosis the calcium was reduced in amount. They say: "The pathological lesion of acne is in the sebaceous glands of the hair follicles while in furunculosis the sweat glands become infected. It is of interest to note then that in one patient with folliculitis barbæ in which the hair follicle is involved the amount of calcium in the blood was increased."

Independently of Thro and Ehn we examined the blood from a number of patients with acne and other skin conditions for calcium by the method of Halverson and Bergeim. Our results did not show any increase in the calcium content of the blood in acne vulgaris.

Psoriasis. In a number of cases of psoriasis investigated no change in the blood chemistry so far as the nitrogen distribution goes was observed. A number of the patients showed a state of mild acidosis. A remarkable increase was observed in the non-protein sulphur of the blood. We shall reserve for a future communication the discussion of this subject.

No.	CO_2.	Urea N.	NPN.	Creatinin.	Glucose.
1 . . .	44	10	22	0.85	0.1
2 . . .	62	..	17	1.1	0.11
3 . . .	66	15	25	1.7	0.1
4 . . .	52	20	33	1.25	0.09
5 . . .	38	11	27	1.1	0.1
6 . . .	44	10	22	0.85	0.1
7 . . .	38	12	29	1.5	0.22
8 . . .	53	..	..	....	0.074
9 . . .	44	12	24	1.0	0.1

Conclusions. 1. In mild cases of eczema no disturbances were observed in the chemical composition of the blood nor in the condition of the hydrogen-ion concentration of the body fluids. In eczema accompanied by other metabolic derangement the deviation of the blood chemistry was due to the metabolic diseases, as, for example, diabetes. In the latter case conditions of acidosis were noticed. In severe diffuse eczema we observed a state of acidosis, an increased ethereal sulphate fraction in the urine, indicative, perhaps, of intestinal putrefaction, but otherwise a normal blood chemistry.

2. No marked deviation in the blood chemistry aside from hyperglycemia was observed in cases of acne vulgaris.

3. In cases of psoriasis the non-protein sulphur of the blood seemed to show larger figures than usual.

4. In one case of xanthoma a marked increase of the blood cholesterol was observed.

5. A mild acidosis seemed to accompany some of our cases of seborrheic eczema, psoriasis, acne vulgaris and urticaria.

ACUTE SUPPURATIVE APPENDICITIS (GANGRENE OF THE APPENDIX) EXPERIMENTALLY PRODUCED.

By Richard J. Behan, M.D., Dr. Med., (Berlin), F.A.C.S.,
surgeon st. joseph's hospital, pittsburgh, pa.

(From the Surgical Department and Pathological Laboratories of St. Joseph's Hospital, Pittsburgh, Pa.)

Acute appendicitis is usually held to be caused by some foreign body which may be a hard particle of food irritating or injuring the mucosa, so that bacteria pass through into the submucous layer and induce an inflammation. The inflammation results in swelling, which interferes with the circulation of the blood in the muscular wall. Continuation of this results in a decrease of nutrition of the wall and consequent death of the tissue. (De Forest.) This is the usual explanation of the cause of appendicitis.

However, if irritation alone is the cause of the inflammation—

1. Why does not inflammation of a similar character occur in the intestine, where the same irritation, but greatly magnified, is present? It is usually answered that the anatomical structure of the appendix is different from that of the bowel, in that it contains much lymphoid tissue. At least such an explanation has been made.

2. An enterolith or rough food particle may be present in the appendix for years without producing inflammation, and this foreign body must in the time of its residence produce numerous abrasions and traumata to the mucosa of the appendix.

If the two preceding statements are correct there must be other causative factors which are more or at least equal in potency to the enteroliths or foreign bodies as a cause of appendicitis. Additional factors are:

1. A fixed or abnormal position of the appendix in relation to the cecum and parietal wall, with associated bands or adhesions binding the appendix to surrounding structures, namely, the lateral abdominal wall, the psoas muscle, the cecum, the ileum and the colon.

2. A disturbed blood supply, due to kinking or obstruction of the bloodvessels.

3. Dislocation of the cecum with distention of the cecal lumen and consequent traction on an adherent appendix.

4. Obstruction of the lumen of the appendix. This seems from our experiments on rabbits to be the most potent factor in causing acute suppurative appendicitis (gangrenous appendicitis.) These experiments were incidental to other experiments on the production of intraperitoneal adhesions. The results of the latter experiments were reported in the American Journal of Medical Sciences, September, 1920.

In the first experiment an attempt was made to determine whether perforation or injury of the mucosa is an active cause of acute appendicular inflammation. A rabbit was operated on February 4, 1917. The abdomen was opened, the appendix was isolated and a subserous suture of linen was introduced circumferentially around the appendix and was tied. A hypodermic needle of large lumen was then introduced into the distal end of the appendix and an attempt was made to remove some of the contents. There did not seem to be any free fluid in this terminal portion of the appendix. After the needle was removed it was possible to express a small amount of the fecal matter from the appendix through the needle opening. This was collected and dissolved in a tube of salt solution and a culture made. The culture was sterile.

On reoperation February 12, 1917, the appendix was inflamed and very red. There were adhesions at the extreme tip to two adjacent segments of the bowel. These adhesions were very firm and were separated with difficulty. They extended, however, only for a short distance and corresponded to the area at which the fecal material had been expressed on to the surface of the appendix. The rest of the appendix was free. The appendix was removed and opened. The lumen of the distal portion was free and showed no abnormality, not being different in any way from the proximal portion. Opposite to the portion where the circular ligature had been applied there was a line in the mucosa which indicated that the circular occluding ligature had at this point cut completely through the muscularis, the submucous and the mucous layers of the walls. It was found in the wall of the appendix. There was not the slightest obstruction. The circular defect in the mucosa must have persisted for a few days, so that there was sufficient time for infection to spread through the mucosa into the submucous tissue and to give rise to an appendicitis. This had not occurred.

Confirmative of this is the result obtained in a rabbit operated on Septemb[illegible] 18, 1917, in whom a subserous ligature had been placed around the appendix. On tying it tightly it cut through the muscularis and mucosa. The rabbit was killed on October 13, 1917.

The appendix was found to be normal. The mucosa was intact except at one place, where there was subserous thickening. No adhesions were present. The ligature apparently had pulled through the mucosa, but had produced no obstruction. The defect in the mucosa, the submucosa and the muscularis had not resulted in inflammation of the appendix.

A further confirmation of the conclusion that injury of the mucosa will not cause acute appendicitis in the rabbit is the operation performed September 19, 1917. Here a subserous ligature was placed around the appendix. It was of very fine linen. On tying, the feeling was present that the suture had pulled through the wall into the lumen. On operation October 12 it was found

that the terminal portion of the appendix was not dilated. On November 10 the abdomen was reopened. The appendix was firmly adherent to the adjacent intestines. The intestines were separated by sharp dissection and the appendix was freed. The appendix was removed. No special change, except the surrounding adhesions, was noted in the appendix. Cultures from the lumen of this appendix were sterile.

To definitely determine whether, in the presence of active bacteria (streptococci and colon bacilli), an injury to the mucosa would lead to an acute inflammation, the following experiment was performed late in November, 1917.

The appendix was denuded and a culture of living streptococci and colon bacilli was injected into it. The denudation of the serosa was about one inch away from the area of the injection and was of such a degree that bleeding ensued.

On December 4, that is, about three weeks after this experiment, the abdomen was opened. There was great difficulty in finding the appendix. It was finally located high up on the right side and apparently firmly attached by adhesions at its base to the posterior wall, so that it could only with difficulty be delivered into the wound. It was found that the serosa was normal in appearance, except at the place where it had been adherent. This adhesion was at the place where the serosa had been denuded. The injection into the lumen of the appendix of active growth of streptococci and colon bacilli may also have had some influence in causing an active inflammatory reaction and the formation of adhesions at the point of denudation. There was no change in the mucosa.

In this case there was a defect in the mucosa at the point where the injection needle had perforated it; still, acute suppurative appendicitis had not resulted.

Even incomplete stasis, in which there is a *partial blocking off of the appendicular lumen, does not in rabbit experiments cause appendicitis* even though fecal material collects in the part distal to the partial obstruction.

This is verified by the experiment of January 9, 1918: A culture was taken from the lumen of this appendix and was found to be sterile. The lumen was then blocked by means of a circular subserous suture. After tying the suture the lumen was not entirely obliterated, so a second suture was applied above the first, about one and a half inches from the distal end of the appendix. On February 10, 1918, the rabbit was reoperated. The appendix was found to be very large. There were a few adhesions to the adjacent bowel at the mesenteric attachment of the appendix. Inspection of the appendix showed a slight constriction at the point of previous ligation. The serous surface of the appendix was smooth and glistening. The appendix was removed. On being opened the appendix, distal to the partially obstructing ligature, was filled

with dark material. The portion of the appendix proximal to the obstruction was free of this material.

The obstruction was not of great moment. It seemed to act as a partial valve, so that material passed through from the bowel to the distal end, but did not easily pass in the opposite direction. The mucosa was not injured.

In this case an *injury to the mucosa of the appendix and a partial obstruction of the lumen had not resulted in appendicitis. If, however, an obstruction totally blocks the lumen and affects the mucosa alone, the submucous area and the muscularis being free, lymph-like fluid collects in the submucous space and increases to such a degree that it will dissect free the mucosa*, as is illustrated in an experiment on a rabbit operated January 20, 1918.

The appendix was occluded by a purse string suture halfway between the tip and the base. The suture was inserted subserosally. Some weeks later the rabbit died.

On opening the abdomen few adhesions were found. There was no free fluid. The abdominal skin wound was infected. The appendix had become enlarged into a mass about 10 cm. x 5 cm. x 5 cm. It was rather tense. The small intestines had spread over it and become adherent in various places. These adhesions were mostly between the mesentery and the surface of the appendix. The place on the appendix where the purse string occluding suture had been inserted was surrounded by rather dense adhesions. The appendicular mass was opened and proved to be a large cyst with very thick walls. The cavity was filled with a thick, whitish material with no odor. On the inner surface was a whitish membrane, very friable. Beneath this membrane was a smooth surface, the muscularis. Attached to the place where the purse string suture had been placed, *i. e.*, at the point where the appendix was occluded, a mass of tissue was hanging free in the cavity. This was regarded to be the mucosa, which had evidently been undermined and loosened from the subjacent tissues by the fluid which had collected in the submucous space. Communication between the proximal (normal) appendicular lumen and the occluded distal lumen was obliterated. (Unfortunately cultures made from this material as well as the fluid itself were lost, so that a complete determination of its character could not be made.)

In the above case the muscularis was not included in the obstructing ligature. If it had been severe, inflammatory reaction likely would have followed. This occurred in an experiment on November 6, 1917, when a circular suture of linen was placed around the appendix subserosally and drawn snug enough to make a marked constriction. The meso-appendix was not touched. In two days the rabbit died. The appendix was found to be very thick and infiltrated, especially in one place where it had rested on the mesentery and on an adjacent segment of bowel. The infiltration and inflammation

were only present in the segment distal to the point at which the circular suture had been placed. From the surface colon bacilli were cultured. On opening the appendix the lumen was greatly dilated in the segment beyond the point of constriction and was filled apparently with pus or a material which resembled pus. The mucosa and muscularis beyond the point of obstruction were destroyed. There seemed to be a complete blocking of the lumen at the point of obstruction. Proximal to the obstruction the mucosa and muscularis were apparently normal. The reaction in this case was not quite as severe as in the following case, where the appendix was occluded by a double subserosal ligature of linen. This resulted in gangrene of the appendix and death the next evening.

This rabbit was operated on October 11, 1917. The proximal part of the appendix was occluded by a ligature passing around the appendix beneath the serosa. This ligature was of linen and was doubled. After the operation the rabbit did not seem to be especially ill, but he died in about twenty-four hours after the operation.

Autopsy showed that the contents of the lower portion of the abdominal cavity were firmly attached to the peritoneal covering of the abdomen. In many places in the lower abdomen, quantities of fibrinous exudate were present. The entire lower portion of the abdomen was filled with a mass of inflamed intestines. In the right lower quadrant there was a considerable quantity of free fluid, serofibrinous in character. The appendix was adherent to the adjacent intestine. It was withdrawn from the abdominal cavity and was found to be gangrenous. The gangrene was most marked at the distal extremity beyond the point at which the circular ligature had been placed at the time of operation.

The gangrene was indicated by a dark discoloration. There was a distinct line of demarcation. It had extended up underneath the serosa for about one inch proximal to the point where the ligature had been applied. The meso-appendix also was very red and inflamed and rather dark in color. On dissecting the meso-appendix the two layers were found to be separated by a thick bloody exudate. This exudate extended back beyond the junction of the meso-appendix with the mesocolon and also beyond the point of the juncture of the appendix with the cecum. The lumen of the appendix was not opened. The appearance of the appendix indicated that there had first been a destruction of the tissues of the appendix lying distal to the ligature. Then that this destruction had induced infection of the supplying bloodvessels (sufficient to cause thrombosis) with gradually progressing necrosis and associated gangrene of the appendix, which (in this instance) extended toward the base.

The serosa of the appendix distal to the ligature was intimately involved in the inflammatory reaction, while the serosa of the appendix proximal to the ligature did not seem to be involved.

Acute suppurative appendicitis (gangrene) in this case was apparently caused by strangulation of the mucosa, submucosa and muscularis.

On December 22, 1917, a circular ligature was inserted around the appendix of a rabbit so that it blocked the lumen. It was tied tight. Some bleeding occurred at the point of ligation.

In this rabbit, which died two days later, the appendix showed some necrotic areas of the mucosa. On the external surface of the appendix there was a considerable deposit of fibrin-like material. This deposit was between the bowel and the appendix. The appendix was gangrenous. This is a further confirmation.

In order to determine what effect, if any, blocking of the circulation of a restricted portion of the appendix may have on the portion of the appendix supplied by the obstructed vessels, an experiment was performed in which the circulation to the appendix was partly restricted, with a kink of the appendix resulting, with no structural changes in the appendix. In this experiment the abdomen was opened and the appendix was found and brought out of the peritoneal cavity. About one inch from the distal end of the appendix the supplying vessels in the meso-appendix were surrounded by a ligature in a direction parallel to the meso-appendicular border of the appendix. The long vessels which run parallel to this border were also caught in the ligature. The ligature was now tied, entirely blocking this portion of the circulation. A second ligature was then placed farther up toward the mesocecal junction, so that at least one-half inch or three-fourths of an inch of the meso-appendix near to the place where it joins to the mesocolon was included to the ligature. The appendix was now replaced in the peritoneal cavity. This rabbit seemed to be perfectly well until two weeks after the operation, when it would not eat and seemed to be apathetic. Finally it died.

On autopsy few adhesions were present in the abdominal cavity. The appendix showed no special inflammation. There was a rather well-marked kink present where the vessels had been tied, but this did not seem to produce any stricture or other change in the appendix at this point. The appendix was removed. The above experiment was repeated several times with the same result.

The absence of structural change in the appendix is interesting, showing in this experiment that in the rabbit *partial destruction of the circulation in the meso-appendix is not necessarily conducive to inflammation or to any great change in the appendix itself.* Apparently the adjacent collateral circulation in the meso-appendix, or the circulation in the wall of the appendix is able to carry on nutrition, so that necrosis does not occur. It may be that the nutrition of the appendix is carried to a great extent through the vessels which are in the muscular or subserous layer of the appendix. Otherwise it would be difficult to explain why gangrene should take place when the muscular, the subserous and the mucous coats are strangulated, while no apparent change results when the cir-

culation is blocked. Gangrene is usually thought to be due to bloodvessel obliteration.

If the disturbance of the blood supply in the meso-appendix does cause gongrene of the appendix the only supposition for the origin of the gangrene in the appendix is, that the gangrene is due to a rapidly extending inflammatory process in the appendicular lumen, involving the muscular, mucous and submucous coats and quickly spreading into the veins thus producing thrombosis and gangrene of the ascending type, moist in character.

RÉSUMÉ. From our experiments on rabbits it was noted that the only time acute inflammatory reactive changes in the appendix occurred was when the lumen of the appendix was entirely obstructed, with strangulation of the mucous, the submucous layer and the muscularis.

Obstruction to the lumen alone apparently resulted only in a collection of fluid between the mucosa and the muscularis in the submucous space, so that a cyst of the appendix was formed. However, when the obstruction extended beyond the mucosa and included the submucosa and muscularis a very marked reactive inflammation resulted, and gangrene of the appendix with sepsis and death of the rabbit took place.

The presence of bacteria in the lumen of the appendix is not, in the rabbit, a necessary prelude to inflammation. Gangrene of the appendix may occur even when previous cultures from the lumen of the appendix showed no bacterial growth; however, when inflammation had already taken place and the surface of the appendix was inflamed, cultures from the surface of the appendix gave growths of colon bacilli. This inflammation in our experiments apparently did not primarily result from thrombotic changes in the blood vessels of the meso-appendix. The blood vessels of the meso-appendix may be partially blocked and no pathological change occur in the appendix. The pathological variation or change evidently took place both in the lumen and in the coats of the appendix and led to deadly inflammatory reaction in the walls of the appendix. This reaction was always distal to the obstruction which we had erected.

How closely the above processes may simulate those which occur in the human is problematical. The appendix of the rabbit is longer, larger and has a slightly different arrangement of blood supply than has the human appendix. However, clinical observation seems to confirm, at least to a degree, that the above observations may also be applied to man.

Obstruction of the appendix may result clinically when a foreign body is present in the appendix and obstructs the lumen at some point where there has been a constriction. Gradual swelling of the mucosa may be sufficient to produce a strangulation of the submucous and the muscularis layers the same as occurs when a ligature or clamp is applied. When this stage is reached gangrene supervenes.

AN AUSCULTATORY SIGN OBSERVED IN ACUTE ABDOMINAL DISEASES.

By Paul W. Aschner, M.D.,

ADJUNCT SURGEON AND ASSISTANT IN SURGICAL PATHOLOGY, MOUNT SINAI HOSPITAL, NEW YORK.

(From the Surgical Services of Howard Lilienthal, M.D., and Edwin Beer, M.D.)

The methods employed in examination of the abdomen are commonly limited to inspection, palpation and percussion. Cabot says: "Our methods are crude and inexact compared to those applied to the chest. Auscultation is of practically no use." Gerhardt speaks of a single sound and at times a systolic murmur heard over the abdominal aorta. He describes friction sounds heard over the liver, the spleen, or tumors, and over the intestines in case of peritonitis. He mentions the rare finding of signs due to sacculations of air and fluid, as in subphrenic pyopneumothorax. No additional data are found in the works of Sahli or of Brugsch and Schittenhelm.

Believing that some information might be obtained by examining with the stethoscope, auscultation was applied to the abdomen in acute cases. Most of these were cases of appendicitis.

In some patients examined in this way it was found that the heart sounds and the inspiratory murmur were audible over three or four of the quadrants. The heart sounds were somewhat distant and reminded one of the fetal heart sounds familiar to the obstetrician. The inspiratory murmur was audible at times with quiet respiration, at other times only when the patient was requested to breathe more deeply. When the abdomen was opened the peritoneal cavity of patients presenting these auscultatory signs was found to contain free pus, seropurulent fluid or blood (as in a case of ruptured tubal pregnancy). After a number of such experiences it became apparent that the physical sign had some significance and the keeping of data on this point was begun. The unreliability of shifting dulness as a sign of free fluid in the acute abdomen is well known. If this auscultatory sign should prove significant of free fluid it would be of clinical value.

It was suggested by a colleague that cases of ascites ought to present the sign, but it was deduced that it would not be present for the following reason: Ascites is a gradual accumulation of fluid causing stretching of the parietes, whereas the sign appears with a sudden accumulation of fluid under tension. The physical conditions are different. Several cases of ascites in the medical services were examined with negative auscultatory findings in every instance.

Many patients in the surgical wards without abdominal disease were examined and in no instance was the sign described encountered.

Occasionally the heart sounds were audible in the epigastrium or a systolic tone was heard over the abdominal aorta.

Analysis of Case Records. 1. Cases with positive auscultatory sign and positive findings at operation, 17.[1]

Of these 17 cases the heart sounds and inspiratory murmur were heard in all four quadrants in 10, in three quadrants (right and left upper and right lower) in 3, in two quadrants (right and left lower) in 3, in two quadrants (right upper and lower) in 1 case. The patients' ages ranged from one to fifty-five years. Shifting dulness was made out in only 2 cases. In 7 cases the usual symptoms and signs of peritonitis (facies, general abdominal rigidity, rebound tenderness) were present. In 8 cases the presence of peritonitis was not considered or seemed very doubtful.

In 2 cases (both infants) aspiration of the abdomen with needle and syringe yielded pus. (For the use of this procedure I am indebted to Dr. Howard Lilienthal.) Both of these were operated upon because smears of the pus excluded a primary pneumococcus peritonitis.

The findings at operation in these 17 cases were as follows: In every one of this group free pus or seropurulent fluid was found in the peritoneal cavity. In 15 cases this was due to an acute appendicitis with perforation in 7. In 1 it was due to an acute postabortive metritis. (Examined through the courtesy of Dr. Hiram N. Vineberg.) In another the underlying condition was a purulent cholangitis due to common duct stones. The gall-bladder itself showed only chronic inflammatory changes, the peritonitis apparently resulting from extension through the duct walls.

2. Cases with negative auscultatory sign and negative findings at operation, 12.

In 3 cases of marked abdominal distention in acutely ill patients the absence of the auscultatory sign was of interest, as the possibility of the production of the sign by distention had come up for discussion. The cases were: (1) Incarcerated femoral hernia, (2) obstructing carcinoma of splenic flexure, (3) acute gangrenous appendicitis with reflex ileus.

In 4 cases of acute gangrenous appendicitis and 1 of acute pancreatitis the general symptoms, the widespread abdominal rigidity or marked rebound tenderness strongly suggested active peritonitis. In none was the auscultatory sign present and in none was fluid found in the peritoneal cavity at operation. In a case of penetrating bullet wound in the right hypochondrium with marked rigidity of the upper abdomen the sign was absent and the subsequent course excluded intraperitoneal hemorrhage or perforation

[1] An additional case was recently examined on the pediatric service of Dr. Henry Heiman. It was a case of pneumococcus peritonitis in a child of three years. The auscultatory sign was present and the diagnosis proved by aspiration and culture of the pus obtained from the abdominal cavity.

of a viscus. In the case of a child run over by an automobile the physical findings strongly suggested intraperitoneal injury. The auscultatory sign was absent and subsequent course and operation proved the injury to be confined to the right kidney with production of an "extrarenal hydronephrosis."

In a case of perirenal hematoma of unknown origin and in a case of suspected tubal pregnancy, in both of which the sign was absent, operation proved the peritoneal cavity to be free of blood or fluid.

3. Cases in which heart sounds were heard in one or both upper quadrants only, 4.

Transmission of heart sounds to one or both upper quadrants was regarded as of doubtful significance because of the following cases: In one case of transmission to both upper quadrants a small amount of seropurulent fluid was found in the pelvis. In another case with similar signs no free fluid was found. In a case with heart sounds audible in the left upper quadrant only an acutely inflamed retrocecal appendix was found with no free fluid. In a case showing transmission of heart sounds and inspiratory murmur to the upper quadrants only a small amount of clear serum caused by a twisted Meckel diverticulum was encountered.

4. Cases with negative auscultatory sign and positive findings at operation, 3.

In 2 cases with negative auscultatory findings a small amount of serum was present in the pelvis. In neither case could a peritonitis really be said to exist. In a child of seven years brought to the hospital *in extremis*, with a small, rapid and at times imperceptible pulse with shallow respirations, forty to fifty per minute, auscultation was negative. Operation revealed a diffuse purulent peritonitis. The heart sounds were barely audible over the precordium, and this in itself precluded transmission to the abdomen.

5. Cases with positive auscultatory sign and negative findings at operation, 2.

One of these was a woman, aged fifty-two years, with a markedly distended colon and an empyema of the appendix without free fluid in the abdomen. The second was a boy, aged ten years, with an acute gangrenous appendicitis, considerable distention of the small bowel, but no free fluid.

These 2 cases prove that the sign is not an infallible one and may be occasionally caused by distention of the bowel.

Conclusion. Auscultation of the abdomen in acute conditions accompanied by seropurulent or purulent exudation into the peritoneal cavity reveals a physical sign which is present in a high percentage of cases. Of 20 such cases the sign was positive in 18, doubtful in 1, and negative in 1. The last was an infant *in extremis*. In only 2 of the cases was shifting dulness demonstrable. In 8 cases the symptoms and usual physical examination did not suggest the presence of peritonitis.

In 2 cases presenting the sign and not showing the expected peritonitis marked intestinal distention was present. In 3 other cases of distention without peritonitis the sign was not present. Further observations will be necessary to determine how much this factor vitiates the value of the sign.

Only 1 case of intraperitoneal hemorrhage, a ruptured tubal pregnancy, was observed, and it showed the sign. Observations on traumatic conditions of the abdomen will be of interest in this connection.

A CONTRIBUTION TO THE STUDY OF LETHARGIC ENCEPHALITIS IN ITS RELATION TO POLIOMYELITIS.[1]

By M. Neustaedter, M.D., Ph.D., John H. Larkin, M.D.,

and

E. J. Banzhaf, Ph.D.,

New York.

(From the Strecker Laboratory, City Hospital, and the Research Laboratories, Department of Health, New York City.)

Since lethargic encephalitis, so called, has appeared in pandemic form it has been most intensively studied by pathologists and clinicians the world over. As a result of these studies it has not been possible to arrive at a definite conclusion whether it is a distinct disease entity or another phase of epidemic poliomyelitis. The problem uppermost in the minds of investigators now is how close is the relation between lethargic encephalitis and poliomyelitis? In this connection we have taken up the study of the effect of serum of patients recovered from lethargic encephalitis upon the virus of poliomyelitis *in vitro*.

It is a well-established fact, as was shown by Flexner and Lewis, Netter and Levaditi, Roemer, and Anderson and Frost, that serum of patients recovered from poliomyelitis neutralizes virus of poliomyelitis *in vitro* and also protects monkeys from the disease when injected with such a mixture. It is also known that normal human serum does not, as a rule, neutralize the virus.

Following are the protocols of our experiments:

Experiment 1. March 6, 1920, Macacus A was injected intracerebrally with 0.5 c.c. of a mixture of poliomyelitis virus and serum of patient Miriam S., aged sixteen years, three months after recovery from lethargic encephalitis, prepared in the following manner:

[1] Read before the Association for Research in Nervous and Mental Diseases, December 29, 1920, New York City.

COMPARATIVE RESULTS OF NEUTRALIZATION EXPERIMENTS WITH POLIOMYELITIS VIRUS AND SERA OF PATIENTS CONVALESCENT FROM POLIOMYELITIS AND LETHARGIC ENCEPHALITIS

Investigators.	Monkeys. Virus and serum mixtures.	Result.
Flexner and Lewis	5 polio virus + human convalescent polio serum	4 protected. 1 paralyzed, living.
	3 polio virus + human suspected polio serum	1 protected. 2 paralyzed and died.
	7 with nine injections of polio virus + normal human serum of adults and children	3 paralyzed and died. 5 protected. 1 died; no paralysis; no polio lesions.
Netter and Levaditi	4 polio virus + human convalescent polio serum	4 protected.
	1 control polio virus + normal salt solution	1 paralyzed and died.
	3 polio virus + human convalescent polio serum	3 protected.
	1 control, polio virus + normal human serum	1 paralyzed and died.
Roemer	3 polio virus + human convalescent polio serum	3 protected.
	1 control, polio virus + normal salt solution	1 paralyzed and died.
	3 polio virus + human convalescent polio serum	3 protected.
	1 control, polio virus + normal newborn infant serum intracerebrally and 5 c.c. pure virus intraperitoneal.	1 paralyzed and died.
	2 controls, polio virus + normal newborn infant serum	1 slightly paretic; recovered 1 paralyzed and died.
Anderson and Frost	1 polio virus + human convalescent polio serum	1 protected.
	10 polio virus + human suspected polio serum	7 protected. 1 paralyzed and died. 2 paralyzed; survived.
	2 controls, polio virus + normal human adult serum	2 paralyzed.
	5 polio virus + normal human adult serum	3 protected. 2 paralyzed and died.
	3 polio virus + normal human adult serum	3 paralyzed.
Authors' cases	5 polio virus + human convalescent Leth. encephalitis serum	5 protected.
	4 controls, polio virus + human normal adult serum	1 paralyzed and dying. 1 paralyzed; survived. 2 paretic, recovered.
	1 control, polio virus + normal salt solution	1 paralyzed and dying.

0.125 c.c. of a 5 per cent suspension of brain and cord of a monkey that died of poliomyelitis—obtained through the courtesy of Dr. Amoss from the Rockefeller Institute—were mixed with 1.25 serum

of the above patient and incubated at 37° for two hours and kept in the refrigerator for twenty hours.

Result. The animal remained well without any visible ill-effects until April 21, when it was found dead. The autopsy showed that the cause of death was tuberculosis.

Control. Macacus B was injected in the same manner with 0.5 c.c. of a mixture of the same virus and in the same proportion with normal adult serum prepared as above.

Result. The animal became paralyzed on the eighth day in the right upper and lower extremities, but survived until October, when it was anesthetized and autopsied.

EXPERIMENT 2. May 18, 1920, Macacus E was injected intracerebrally with 1 c.c. of a mixture of equal parts of a 5 per cent suspension of Rockefeller Institute poliomyelitis virus and serum of patient, Dave J., aged thirty years, recovered from lethargic encephalitis since February 20, 1920. This mixture was incubated at 37° for one hour and twenty minutes and kept on ice for nineteen and a half hours.

Result. The animal never suffered any ill-effects and remained perfectly well until August 25.

Control. Macacus D was injected in the same manner with 1 c.c. of a mixture of equal parts of the above virus and normal adult serum prepared as above.

Result. May 24 the animal was found ill sitting in a corner of the cage. May 25 the animal was paralyzed in all four extremities and muscles of the neck with shallow respiration. Anesthetized and autopsied. Macroscopic changes were characteristic of poliomyelitis.

EXPERIMENT 3. June 22, 1920, Macacus F was injected intraspinally with 4 c.c. of a mixture of equal parts of a 2.5 per cent suspension of virus of monkey D and serum of Dr. G., aged fifty-five years, suspected of having had lethargic encephalitis and was left with a paralysis of facial nerve, with complete reaction of degeneration. This mixture was incubated at 37° for two hours and kept on ice for twenty-two hours.

Result. The animal suffered no ill-effects and remained well up to November 5.

Control. Macacus G was injected as above with 4 c.c. of the same virus mixed with equal parts of normal NaCl solution and incubated as above.

Result. June 28 the animal was ill and refused food.

June 29 paralyzed in all four extremities and muscles of the neck. Anesthetized and autopsied. Macroscopic and microscopic changes were typical.

EXPERIMENT 4. October 8, 1920, Macacus K was injected intracerebrally with 1.5 c.c. of a mixture of equal parts of an 8 per cent suspension of poliomyelitis virus of M. E. and serum of patient

M., of Dr. Foster Kennedy's service in Bellevue Hospital, six months after recovery from lethargic encephalitis, incubated for two hours at 37° and kept in the refrigerator for twenty-two hours.

Result. The animal suffered no ill-effects and is well today.

Control. Macacus L was injected the same way with 1.5 c.c. of a mixture of equal parts of the above virus suspension and serum of a normal adult, prepared as above.

Result. October 14 the animal was very ill; the left upper extremity was paretic. October 16 both hind limbs were paretic. October 19 the animal recovered from pareses and is well today.

EXPERIMENT 5. October 28, 1920, Macacus M was injected intracerebrally with 1.5 c.c. of a mixture of equal parts of a 10 per cent suspension of poliomyelitis virus of M. E. and serum of Mary S., aged sixteen years, a patient of Dr. Foster Kennedy, from the service of Bellevue Hospital, and originally observed by Dr. Tilney and described by him as Case IV in his book on *Lethargic Encephalitis*. The patient is at present in the neurological service of the City Hospital. This mixture was incubated at 37° for two hours and kept on ice for twenty-two hours.

Result. The animal remained well without having suffered any ill-effects at any time.

Control. Macacus N was injected in the same manner with 1.5 c.c. of a mixture of the above virus suspension and equal parts of serum of an eighteen-year-old laboratory helper in the laboratory for clinical pathology of Cornell Medical School, who claims that he was never ill. This mixture was prepared in the same manner as the one above.

Result. November 2 the animal was ill and paretic in the right upper extremity and showed also a slight hypotonia in the right lower extremity. The same condition still prevails today.

EXPERIMENT 6. In order to establish whether some of the animals that were protected by the convalescent encephalitis serum, were refractory Macacus E was injected intracerebrally with 1 c.c. of a 5 per cent suspension of brain and cord of Macacus G on August 25, about three months after the initial injection.

Result. August 31 the animal was found paralyzed in all extremities and dying. Macroscopic and microscopic changes were characteristic of poliomyelitis.

EXPERIMENT 7. Monkey M was injected intraspinally, January 3, 1921, with 2 c.c. of a 5 per cent suspension of poliomyelitis virus.

Result. January 11 the animal became paralyzed in all the extremities and died that night. Macroscopic and microscopic findings were characteristic.

It should be noted here that all sera used proved Wassermann negative; that for each control serum of a different person was used.

Since we have mentioned above the reports of Flexner and Lewis, Netter and Levaditi, Roemer, and Anderson and Frost on neutrali-

zation experiments with mixtures of poliomyelitis virus and serum of frank and suspected cases of poliomyelitis, it may not be out of place to compare their results with ours.

Flexner and Lewis[2] by their experiments show that out of 5 monkeys injected with a mixture of poliomyelitis virus and serum of convalescent poliomyelitis patients in proportion of 1 c.c. serum and 0.1 and 0.3 c.c. virus respectively, 4 were completely protected and 1 became paralyzed, but survived, retaining the paralysis.

Of 3 monkeys injected with virus and serum of suspected cases of poliomyelitis, 2 developed typical paralyses and died, and 1 was completely protected.

Of 7 animals with nine injections of virus with normal human serum of adults and children, 3 died with the typical picture of poliomyelitis, 3 were completely protected and 1 died twenty-seven days after the injection without any paralyses, and no changes in the cord or brain characteristic of poliomyelitis were found.

Netter and Levaditi[3] report that in their first series 4 monkeys were injected with 0.25 c.c. of a mixture of equal parts of virus and serum of recovered poliomyelitis patients. The 4 animals were protected. One control was used for this series and injected with virus in normal solution. This animal became paralyzed on the seventeenth day. In the second series they injected 3 monkeys with virus and serum of recovered poliomyelitis patient and all 3 animals were protected. In this experiment they have also used one control, but this time the virus was mixed with normal adult human serum. The control became paralyzed on the seventeenth day.

Roemer[4] reports a series of experiments in one of which he used one control for 3 virus-immune-serum injected monkeys. The 3 monkeys were protected. The control was injected with virus in normal salt solution and this animal became paralyzed and died in thirteen days. In the second series 3 monkeys were injected with virus and immune serum and all 3 animals were protected. Of the 3 controls in this series 1 was injected with virus and normal newborn infant serum intracerebrally, and in addition 5 c.c. pure virus intraperitoneally, and this control animal became paralyzed on the thirteenth day and died on the twenty-third day. The 2 other controls were injected with virus and normal newborn infant serum only. Of these 2 controls 1 became paralyzed and died on the fourteenth day and the other was paretic in the right upper extremity on the seventh day, but soon recovered and remained well. In two further suspected cases the virus and serum animals as well as the controls never showed any ill-effects.

Anderson and Frost[5] have in their series of experiments injected

[2] Flexner and Lewis: Quoted by Peabody, Draper and Douchez, Monograph 1, Rockefeller Institute, 1912, p 16.

[3] Netter and Levaditi: Société de Biologie, 1910, pp. 617–885.

[4] Roemer: Die epidemische Kinderlaehmung, Berlin, 1911.

[5] Anderson and Frost: Jour. Am. Med., Assn., 1911, lvi, 663.

the monkeys with 1.1 c.c. of a mixture of 0.5 c.c. of each serum and 5 per cent suspension of virus and 0.1 c.c. fresh normal serum. One monkey received an injection of virus and serum of a convalescent adult poliomyelitis patient. This animal was protected. Ten monkeys were injected with virus and serum of suspected cases of poliomyelitis. Of these 7 were protected, 1 became paralyzed and died and 2 became paralyzed and survived. As a control to this series of 11 monkeys 2 were injected with virus and normal human adult serum. Both animals became completely paralyzed. Two additional series of monkeys were injected on December 24, 1910, one month and eleven days after the first series of injections, and again on January 12, 1911, nineteen days after the second series. Whether one could properly speak of the two series as controls to the first series injected November 13, 1910, or not the results were as follows: In the December 24 series 5 monkeys were injected with virus and normal serum. Of these 3 were protected and 2 became paralyzed and died. In the January 12 series 3 monkeys were reinjected with virus and normal human serum of the cases that were not protected in the earlier series. All the 3 animals became paralyzed.

To summarize we would say that 5 monkeys were completely protected from poliomyelitis by sera of patients convalescent from 4 undoubted cases of lethargic encephalitis and one suspected case, and secondly, that our results compare favorably with the results of other investigators in the neutralization experiments of poliomyelitis virus and convalescent human poliomyelitis sera.

We wish to thank Dr. William C. Thro, Miss Matilda W. Harms and Dr. Foster Kennedy for their assistance and encouragement, and Dr. Amoss for his kindness in providing us with poliomyelitis virus.

MERALGIA PARESTHETICA (ROTH'S OR BERNHARDT'S DISEASE): WITH THE REPORT OF FIVE CASES; THREE CASES OCCURRING IN THE SAME FAMILY.

By Hyman I. Goldstein, M.D.,

ASSISTANT IN MEDICINE, GRADUATE SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILA., PA.

Most of the literature on the subject of meralgia paresthetica, (Parästhesie der Hautnerven am Oberschenkel, paresthesie de Bernhardt, meralgie de Roth, Bernhardt's Sensibilitätsstörung) has been written during the past twenty years. A number of cases were reported during 1895 and 1900 in America, France and Germany.

At the February (1900) meeting of the New York Neurological

Society, Dr. Philip Meirowitz showed two cases, one in a man, forty-eight years, a presser of coats, the condition was probably due to the long-continued pressure against the thigh, standing at a table in ironing coats for twenty years, thus affecting the external cutaneous branch of the femoral nerve. There was anesthesia, tactile hyperesthesia, and at the lower part of the affected area the touch of the finger was painful.

The other case was a man, aged forty-seven years. The paper by the late Dr. Musser and Dr. Sailer is very complete. They were able to collect 90 references on the subject, and report 10 of their own cases in the AMERICAN JOURNAL OF THE MEDICAL SCIENCES for January, 1900. Dr. Edwin Bramwell exhibited a case of Bernhardt's Sensibilitätsstörung, or meralgia paresthetica, March 5, 1902, before the Medico-Chirurgical Society of Edinburgh. The patient was a a miner, aged forty-three years; for eighteen months he had suffered from pain over the right hip and over the lower part of the right thigh anteriorly, also from a feeling of coldness on the outer side of the right thigh. The pain was greatly increased on walking and incapacitated him from work. He had not had rheumatism nor syphilis. The condition was attributed to sleeping on hard boards in damp clothes. A relative cutaneous anesthesia was present on the outer side of the right thigh, while there was marked tenderness on pressure over a point an inch and a half below and just external to the right anterior-superior iliac spine. The patient's symptoms were obviously referable to the right external cutaneous nerve. No improvement resulted from rest in bed and faradism. Thomson cut down on the nerve at the level of Poupart's ligament and excised three inches. The nerve and its relations appeared to be normal. The pain immediately disappeared. No degenerated fibers were found in sections stained by the methods of Busch and Weigert. He considers meralgia paresthetica a distinct clinical entity. The pathology is obscure. It may be a neuralgia or a neuritis. Roth has recorded 15 cases. The condition is not generally recognized, and it is important to remember this entity in making a differential diagnosis.

In Miller's case, corset-pressure appeared to be the causative factor, and cutting out a section of the corset cured the patient. Some of the reported cases have been improved with faradism. Resection of the nerve is to be done as a last resort in severe cases. There seems to be no definite causative factor of the disease. It appears to be much more common in men than in women. Influenza, gout, syphilis, corset-pressure, table-pressure, hernial truss or belt, alcoholism, constipation, pregnancy, traumatism, long-standing, typhoid fever, rheumatism, diabetes, obesity and hereditary influence have all been mentioned as possible or probable factors in the causation of this disease. In one case with autopsy there was found

a spindle-form swelling in each nerve at the point where it crossed the crests of the ilia. In these regions there was evidence of neuritis and perineuritis. The spinal cord in this case showed slight sclerosis in the posterior columns.

Warda found a swollen tender nerve on palpation in one of his cases. There is probably some lesion of the external cutaneous branch of the femoral nerve in these cases.

The late William Osler read a paper on this subject before the Philadelphia Neurological Society in 1897 and reported 3 cases of monocrural paresthesia which he believed to be exaggerated forms of this disease.

Roth, who wrote a short monograph on this disease, reported 14 cases (1895). Roth states that in all of his patients the area of pain has been the same—that is, in the distribution of the external cutaneous nerve. A burning sensation may extend at times over the whole thigh. In 5 of his 14 cases the condition was bilateral. Roth believes there may be some compression of the nerve either in its passage under the psoas muscle or where it runs close to the anterior-superior spine of the ilium.

Musser and Sailer were able to collect from the literature 89 cases, and they think it is not a very common disease.

Sabrazes and Cabannes collected 62 cases. Finally, Musser and Sailer's definition for this condition is "a disturbance of sensation on the external surfaces of the thigh, characterized by various forms of paresthesia, associated with dissociation and more or less diminution of sensation." In the 99 cases found (including their own 10 cases) 75 were in men and 21 in women; in 3 the sex was not stated. Ten of the patients were physicians.

Mary Damon reported an interesting case in a school-teacher, aged thirty-eight years. She was rather overfat. She had an attack of epidemic grippe in December, 1900.

There was excessive sensitiveness just below the anterior-superior spine and over an area 8 cm. long over the anterior crural region. There was hyperalgesia throughout. At individual spots in the regions supplied by the ilio-inguinal, iliohypogastric, external cutaneous and middle cutaneous nerves, a single touch sent pain flashing long distances through other branches of the plexus.

Roth was, I believe, the first writer to report this condition as an independent clinical entity and called it meralgia paresthetica.

Pieraccini, Bernhardt, and Musser and Sailer observed several cases previously but did not report them as distinct clinical entities.

Goldflam reported a number of cases who were arteriosclerotics past middle life. In Musser and Sailer's collection 57 cases occurred between the ages of thirty and sixty years. They include a complete bibliography up to 1900 on the subject. I will therefore add a few additional references from 1900 to 1920.

Case I.—Mrs. Elizabeth K. W., married woman. Has charge of a busy café and restaurant. Aged forty-four years. Had two children, one living and well. One died of membranous croup. Last normal period six months ago. Not pregnant. Had a very free flow; excessive bleeding for nine consecutive periods prior to the last period. Has "hot flashes" and thinks she was badly frightened and shocked when she heard revolver shots close by on New Year's eve, when she began to bleed, the flow from the uterus continued for four hours then stopped. Always well, except for soreness, and numbness and a painful spot low down near the groin, and hip and side of the thigh (left). Complains of poor appetite. Stands on her feet at her work the greater part of the day.

General examination is negative. She has some symptoms of the climacteric.

Blood-pressure. Systolic, 130–140 (auscultatory), diastolic, 90 to 95. An area with the anterior-superior spine of the ilium as the center, the size of the hand, is exquisitely tender to the slightest touch, particularly an area extending about 2½ inches posteriorly and 2½ or 3 inches anteriorly to the superior spine and downward toward the groin and across to the side of the thigh. This sharply defined area, which is an irregular triangle, is surrounded by another area of analgesia and hyperesthesia. This area is not nearly so well defined as the painful tender, "tingling or stabbing" area.

Blood Wassermann is 4 plus.

I advised that a section of the corset extending down to the thigh be cut out, or if possible for her to do without the corset for a while. I also ordered lutein tablets with ovarian residue to be taken one three times a day, and a digestant three times a day. Massage was suggested, if not too painful or annoying, and she was advised not to press or stand against the table or counter in the restaurant and to avoid standing up or excessive walking. Of course, antiluetic treatment is indicated. She was married four times; she is now living with her fourth husband. The four factors to be considered here are (1) her occupation, (2) climacteric, (3) lues, (4) corset or counter-pressure. Neurosyphilis and posterior root involvement must be considered and excluded.

Roth has emphasized several points along the line of the nerve (external cutaneous) where trauma of this character may occur—*i. e.*, mechanical factors are believed by some to be the most important, because the peculiar curve of the nerve and its relation to surrounding structures render it especially liable to compression when the thigh is extended.

Very distressing at times is the extreme hypersensitiveness of the skin over the affected area, so that, as in my case, the slightest touch and pressure even of the clothing is annoying and painful. Souques reports a case in which the pain was so intense that during a spasm morphine was necessary.

Roth's points are (1) just after the exit of the nerve where it passes beneath the psoas muscle; (2) where it curves around below the anterior-superior spine and finally the fibrous canal in the fascia lata. Among the mechanical factors responsible there have been mentioned the pregnant uterus, pelvic tumors, varices, tight bands, direct trauma and flat-foot. Pressure on the nerve by the lower edge of Poupart's ligament was found in one case and the symptoms disappeared after partial section of the ligament. Hereditary influences may play a role.

Miller's case was a young woman, aged twenty-three years. Family history negative. She did office work, standing most of the day. Two years before she noticed a peculiar sense of numbness over the upper and outer side of thigh when standing or walking. Several weeks later she suffered from occasional attacks of burning or stabbing pain in this region. These attacks increased and she stopped work; standing would excite an attack. Pain disappeared on sitting down or lying down. At times the slighest irritation over the affected area would cause her to scream.

Examination. A circumscribed area of tenderness located below and slightly outward from the anterior-superior spine of the ilium. Surrounding this was an ill-defined area of hyperesthesia. No analgesia, anesthesia nor thermalgesia. The area of hyperalgesia was triangular in outline, the upper border forming the base about 5 cm. above the iliac bone and extending from the crest of the ilium to 5 cm. medianward from the anterior-superior spine of the ilium. The apex of the triangle was located at the junction of the lower and middle two-thirds of the thigh. General examination of patient negative.

Lower edge of the corset hooked over the anterior superior spine, pressing into the thigh so that when standing erect it was forced in. Miller advised the patient to cut out a portion of the corset over this region, and the relief in a few days was marked. The attacks of pain entirely disappeared. After a lapse of ten days she complained only of slight numbness occasionally.

S. Sherwell, of Brooklyn, in 1910, reported his own case. For about the last ten years of his life he complained of symptoms of meralgia in the area supplied by the external cutaneous nerve, particularly in the outer and lower two-thirds of his left thigh after exertion—walking, riding and cycling. He felt better on lying down and was made worse on resumption of exertion. Sherwell was sixty years old when making his report. He believes that the condition comes from a constriction or pinching of the nerve as it passes through the tough fasciæ of a muscular individual, giving rise to a "temporary non-essential zoster as it were." He thought a rheumatic tendency would have an aggravating effect on the condition.

W. J. Rutherford reports a dozen cases of this disease that he has

seen in the last ten years. The condition, as he found it, is characterized by mononeuritis of the external cutaneous nerve of the thigh. The special feature of this neuritis which, as the external cutaneous nerve is purely sensory, is unattended by motor disturbance, is dissociated sensation, the deep or protopathic sensibility, through afferent fibers contained within the motor nerve bundles, supplying the muscles being unimpaired. Sensation over the area of distribution of the affected nerve, which, as a rule, can be strictly delimited, is lost, so far as finer sensibility is concerned for slight touch, for perception of points, for heat and cold, and to a certain extent for pain, while deep pressure can be perceived, and a touch on the bare skin is felt as though a layer of clothing intervened or as one might feel a touch on the back of a gloved hand. In old standing cases a distinct cutaneous thickening may be made out locally if a fold of skin is pinched up between the finger and thumb and the skin of the affected area (in some cases at least) begins to grow bald from atrophy of the hair follicles; while, either in association with this, or as a result of the analgesia, the phenomenon of the cutis anserina is lost locally, so that if the patient is examined in a cold room there is no goose-skin or on an area in the upper and outer aspect of his thigh, even though the other parts show this distinctly, with erection of the hairs over the rest of the limb.

Not only is there this anesthesia or rather analgesia, but perverted sensations are present in the affected area. These take the form of shooting pains, of a sensation as though an invisible hand had grasped the thigh, and was screwing around a handful of the flesh, and of a sensation as though scalding water were being poured down the outside of the limb. These sensations are usually of short duration and are of variable onset; they may occur for months on end, or even for years in old standing cases, but are liable to recur again and again on little or no provocation. The etiology of the condition seems to be unknown. Treatment is of little use. Tonics, massage, electric treatment have all been tried and have all failed. The attacks of pain tend to wear off and to become less frequent with the lapse of time.

Cumston (June, 1919), in a brief note on the subject, states that Lenoir has published the results of his studies in 39 cases while Sabrazes and Cabannes have reported 62 cases, making a total of 101 case reports of this interesting affection. Of these 65 occurred in men and 29 in women, the others not stated. In all these 101 cases paresthesia occupied the antero-lateral (external) aspect of the thigh, 38 in the left and 36 in the right. He does not report any cases. No mention is made of Musser and Sailer's excellent review on this subject nor of the more recent reports on this interesting clinical entity.

Comment. In Nartowski's case pain increased during sleep.

The symptoms are very variable. There may be tingling, pain;

this pain is usually worse on standing or walking. There may be numbness or cold or damp feeling. Exquisite tenderness may be elicited at times, as in my case.

V. Lutzenberger, in his own case, thought there was hyperalgesia with anesthesia to cold, later analgesia with anesthesia to heat. This is not as found in some of the other cases reported.

Diagnosis. The diagnosis must be made from neurosyphilis, ordinary neuralgia or neuritis; akinesia algera or apraxia algera; intermittent claudication, hysteria, bone disease, etc., must be excluded.

Prognosis. The course of the disease is variable and very indefinite. It is trivial in nature although very annoying. It does not affect the general health of the patient as a rule.

Treatment. Treatment is not satisfactory. It depends entirely on the cause. Various methods of treatment have been tried without much benefit. Rest, massage, counterirritation, antirheumatics, sedatives, electricity, ultraviolet rays, high frequency, etc., may be tried.

Case II.—Mr. Samuel T., aged forty-five years, white adult male. Patient was a dealer in bottled goods (soda water, seltzer, beer and whisky), delivering box and case goods to customers from a wagon, for several years. Complains of peculiar (paresthetic) sensations over the outer side of the left thigh. This "numbness" or "loss of feeling," as if the side of the limb is "dead" and "does not belong to him," is present over the front and external aspect of the thigh from the iliac crest to just above the knee. The condition comes on after walking or standing a while. When he sits or lies down "it eases up and goes away." At the time he has this peculiar feeling he does not feel any pinch or stick along this area of the left thigh—there is apparent anesthesia and some disturbance of thermal sense. He attributes his condition to bathing in the ocean at Atlantic City in the summer of 1919, because he first felt this trouble the next morning after an ocean dip. He has not gone into the ocean since that day. On standing erect five to ten minutes this "dead numb" sensation appears; pinching and sticking in the area over the upper and outer two-thirds of the thigh is not felt by the patient; there is evidently loss of tactile and pain sense for some minutes. On lying down for a while these pinching and sticking tests become somewhat more sensitive, and he begins to notice them.

He has attacks of slight faintness and feeling of weight and discomfort over the heart. He thinks his "heart is weak" and complains of constipation and belching. Sometimes during these spells he thinks he is going to die and "is scared." The vague dull, aching sensation over the heart comes and goes for the past five years. It comes on especially after some exertion. He informs me that several years ago he was told he had "heart strain" and that the roentgen

ray showed the heart to be enlarged. Sometimes he has pain in the right temporal region.

Examination. Heart: Slightly enlarged; no cardiac murmurs; heart sounds somewhat weak, muffled and slow. Heart-beat, 60. No pulse deficit. No pulsus alternans. Myocardial disease. On hopping across the floor there is a slight increase of the heart-beat to 76 or 80 for a minute or two.

Blood-pressure, 118–115 S. (second visit); 72 D. auscultatory. (First visit: S. 125–130, D–85.)

Lungs: No rales.

Blood Wassermann: Negative on two occasions. *Gums and teeth* need dental attention (pyorrhea).

Urine: Moderate amount of indican present; clear; acid; specific gravity, 1.021; urea, 1.6 per cent, 8 gr. in fluidounce; no albumin; no sugar; no casts; few pavement form epithelia; few leukocytes; no red blood cells, little mucus.

Phthalein renal function test (intramuscular): Thirty per cent at first hour and 20 per cent at second hour, total 50 per cent for two hours. Some distention of abdomen and some fulness of descending colon. Liver apparently not enlarged. Spleen not palpable.

He has always been pretty well except for constipation, the "heart and stomach trouble" and this condition of peculiar "dead numb" feeling of the left thigh. There has never been a true attack of angina pectoris with the typical pain over the heart up to the neck and down the left arm. There have been attacks of pseudo-angina (?) or angina pectoris sine dolore (?). His wife never had any miscarriages.

This case in some respects resembles the case reported by Alfred Gordon (Philadelphia, 1900). In Gordon's case the whole external cutaneous nerve, with both its branches and the cutaneous branches of the crural nerve was affected.

The external cutaneous nerve ordinarily arises from the anterior divisions of the second and third lumbar nerves. Then it crosses the outer border of the psoas muscle, cuts perpendicularly the iliacus muscle, to which it is attached by the aponeurosis, leaves the pelvis through the notch beneath the anterior-superior spine of the ilium, is placed in the double layer of the fascia lata, and at 2 cm. below the spinous process divides into two branches: one, the posterior, passes through the fascia lata and divides into branches to supply the skin of the buttocks; the anterior branch becomes superficial below Poupart's ligament and innervates the skin of the antero-external surface of the thigh from the greater trochanter as far down as the external condyle of the femur. This nerve is therefore (according to Gordon) placed in a muscle indispensable to standing and walking (psoas muscle) and in the fascia lata, the contraction of which in walking presses upon it and stretches it. The musculo-

aponeurotic relation and the superficial position of the nerve expose it to traumatic injuries, especially in individuals predisposed to painful paresthesia. Gordon further states that a slight neuritis, that perhaps would remain latent in any other territory of the nervous system, is marked in the sphere of the anterior branch of the external cutaneous nerve. It is to be remembered that even without any inflammatory condition of the nerve, any infection such as acute rheumatic fever, typhoid fever, streptococcic tonsillitis, etc., may of itself be capable of giving rise to neuralgia in a predisposed individual. The sensation over the external part of the thigh in my patient was similar to that of Gordon's patient, in that he feels at each contact the sensation similar to that of rubber or leather, and as stated, the tactile sensation over this area is very much diminished.

Case III.—Herbert B., white schoolboy, aged eleven years. Has a "burning feeling" over the outer side of the right thigh and in the region of the anterior-superior iliac spine. He has worn a belt for two years. For a short period he had a small area, about 5 x 3 inches on the outer side of the left thigh, in which there was some paresthesia, "burning and stinging." This has now disappeared. A younger brother complains slightly of a similar condition; he also wears a belt all the time.

Seven or eight years ago the boy had measles, influenza and a discharging ear. He also had several attacks of tonsillitis and rheumatism and was dropsical on one or two occasions, due to cardiac decompensation. His adenoids, tonsils and several bad teeth were removed in the fall of 1920. He had an attack of acute articular rheumatism (rheumatic fever) with acute endocarditis in April, 1920.

Examination. April 20, 1920. Mitral regurgitation.

Fluoroscopic and Roentgen-ray examination (by Dr. Roberts) showed the heart to be enlarged a little to the right and to the left.

Lungs: Negative.

Blood: Red blood cells, 3,690,000. White blood cells, 15,800. Polynuclears 73 per cent; small mononuclears 22; large mononuclears 2; transitionals 2; eosinophils 1.

Blood Culture: Sterile at the end of seven days; at the end of the tenth day there developed a slow-growing pneumostreptococcus. This may have been a contamination.

Throat Culture: Streptococcus viridans.

Urine: No albumin; no casts; total solids, 23.3 gm. per liter; urea, 8 per cent, ammonium urates present. Specific gravity, 1.010. Some squamous cells; few renal cells.

Another urine specimen showed no albumin; no sugar; no acetone; no diacetic acid; some bladder epithelial cells; some cylindroids; few amorphous urates; few white blood cells; acid; specific gravity, 1.025.

Another throat culture showed Streptococcus viridans predominating and a few pneumococci and Micrococci catarrhales.

Blood-pressure: S. 90; D. 68 auscultatory (April 27, 1920). Since the removal of the tonsils and adenoids by Dr. Husik the boy has been in much better health, although he still complains of this burning and stinging sensation in the region of the great trochanter, anterior-superior spine of the ilium and along the outer side of the middle and upper third of the right thigh.

Donley's (1904) patient, a primipara, was a white married woman, aged forty-three years. Complained of disability in the left thigh. Gave birth to one child nineteen years ago. About a year ago had an attack of "neurasthenia" for six weeks. She is a woman of high-strung temperament and heavy build. No history of syphilis or alcoholism. Constipation. Climacteric, with flushings, dizziness and palpitation. She injured her right foot by dropping a flat-iron on it twelve weeks ago. Eight weeks later she began to notice a peculiar ill-defined feeling of tingling and numbness accompanied by a sense of constriction on the outer side of the left thigh. Because of the severe injury to the right foot she was compelled to throw as much weight as possible upon the left leg. This sensation was usually absent during rest and appeared shortly after she began to walk or stand, followed by considerable pain compelling her to sit down. At times she also complained of an intense heat, or cold, and damp ("wet cloth") feeling, at other times only the pain, numbness and tingling. She had anesthesia on the outer side of the left side of the left thigh from the great trochanter to the head of the fibula. Pain, temperature, tactile pressure and hair sensations were greatly diminished, particularly those of pain and temperature. Strychnine, massage and galvanism rapidly improved her symptoms, and in three weeks they had completely disappeared. In the cases of Féré and Moller the affection involved the anterior crural nerve and the external popliteal nerve was affected in Sollier's case. In Claisse's case it followed malaria. In one of Musser and Sailer's patients the pressure of a heavy army belt caused the symptoms in both thighs. In my case (No. III) of the little boy the factors to be considered were the streptococcic tonsillitis, articular rheumatism (acute rheumatic fever) and the endocarditis (Streptococcus viridans infection) or the pressure of the belt which he was wearing for two years. He was complaining of the "burning feeling and stinging" for a little while a year or so ago on the opposite (left) thigh, but at present most of this trouble is limited to the outer side of the right thigh. In my case (No. II) of the man the occupation of climbing and jumping from the delivery wagon and carrying the boxes (against the front and side of the thighs), gastro-intestinal intoxication from chronic constipation and the cold sea-water bathing are factors to be considered. In the little boy's case the local

application with friction of methyl-salicylate in an oily iodine vehicle and rest, together with moderate doses of salol, strontium or sodium salicylate or cincophen and fractional doses of calomel with sodium bicarbonate seemed to relieve the condition.

Devic employed salicylic acid in ointment form locally. In Donley's case iodine seemed to be harmful, the iodine causing a painful dermatitis—however, this patient may have been hypersensitive to iodine, iodoform and other such drugs, and this one case does not prove that "counterirritation is harmful in these cases," as is stated by Donley. In three of my cases mild local applications and counterirritation seemed to do good.

Osler's first case occurred in a healthy, vigorous man, aged sixty years. The second case was in a healthy looking man, aged thirty-two years, who for a month complained of numbness and queer feelings in the left leg. Osler thought his first case, in the early stage, suggested akinesia algera (Moebius), in which painful sensations in the muscles follow the slightest movement, in consequence of which the patients may be bedridden and helpless. Osler says he "has never seen a typical case of paresthetic meralgia," and then goes on to report the "three remarkable instances of monocrural paresthesia, which are possibly exaggerated forms of this trouble" (March, 1897). Osler's third case occurred in a southern college professor aged thirty-seven years. He was a very nervous man and had worked hard. He complained of a sensation of numbness, burning and lifelessness over the hollow of the right foot; later this sensation extended up the leg almost to the knee. Sitting down and resting lessened the uneasy and numb sensations. He felt worse in cold weather. Walking would cause the sensation of numbness and burning over the leg and thigh. Physical examination was negative.

Walsh states (October, 1900) over 100 cases of meralgia paresthesia have been reported by various observers in the past six years.

Walsh's patient was a neurotic and "neurasthenic" man aged forty-five years, a cabinetmaker, who complained of painful, at times hot, feelings on the outer part of his right thigh. An oval patch of the cutaneous surface 5 x 3 inches was almost anesthetic when pricked with a pin-point. In a corresponding area on the other (left) leg there was a patch of slight hyperesthesia. He felt worse just before a rainstorm. At his work (as a cabinetmaker) he was on his feet all day. His right thigh was constantly rubbed during his work (used a plane a good deal) against the side of the workbench. He always felt better when he sat down, and was entirely relieved upon lying down. In Walsh's case chloroform and iodine locally made him worse, salicylates did no good, rubbing with simple soap liniment did relieve him. He suffered from this condition for several years. Walsh thought it was due to a functional disorder (neurosis) of a localized part of the central nervous system.

Shaw reports (February 13, 1897) 4 cases of this affection: (1) A man, aged fifty years, in whom both thighs were involved, complaining of a feeling of numbness and a burning sensation, and on standing had a painful, stinging sensation on the lower and outer side of the right thigh for ten years. On the left thigh there is some paresthesia in an area 3 x 2 inches but is never painful. (2) A large powerful man, aged fifty years. He had lues twenty-seven years ago. Eats a great deal; bowels are irregular. Complains of a burning sensation in his left leg "like fire" or as if a lot of bees had "stung him." Antiluetic treatment did not seem to relieve him. A year and a half ago he began to have headache in the left temporal region and over the eye, which was constant and made him miserable. The pain in the leg was much increased on walking. His pulse was below fifty and labored. No valvular lesion; the heart appears weak and embarrassed; the sounds are not sharp. Abdomen negative and no gaseous distention of the intestines is present. (3) A female, aged thirty-six years, was treated six years ago for "neurasthenia," from which she recovered entirely. She has one child, eight months old. Complains of a burning sensation about the middle of the outer side of the left thigh. (4) Female, aged sixty years. Also complains of a burning sensation on the left thigh. Shaw thought that "toxemic states" are probably a cause of this condition. He suggests the Turkish bath, electric brush and outdoor exercise.

Case IV.—The little brother (Arthur B.) aged eight years, of my Case III, Herbert B., has had his tonsils and adenoids removed by Dr. D. N. Husik, of Philadelphia about three months ago. He, too, now feels much better. Ten badly decayed teeth were removed at the time of the tonsil operation by Dr. D. E. Cooper, of Camden. No other treatment has been given this boy except to suggest the putting aside of the belt and the performance of the above-mentioned operations.

Case V.—The father, George B., aged thirty-five years, had some "vague pains," but these I attributed to a large direct (right side) inguinal hernia, which was operated upon by Dr. Alfred C. Wood, a short time ago, at the Howard Hospital, Philadelphia. The patient had previously been operated upon for this hernia on two occasions. Pressure of the truss belt was probably the causative factor in this Case V.

Dr. Spiller, of Philadelphia, reported a case of meralgia paresthetica in a middle-aged man complaining of distinct burning and drawing sensation, attended with severe pain in the distribution of the external cutaneous nerve of the right thigh. When in bed, or sitting in a chair, or immediately after standing upon his feet, no unpleasant symptom was noted, but after standing for a short time, or walking, a

distinct burning with drawing pain was experienced. The condition of the muscles and sensation otherwise were normal. The affection had existed one year and was getting worse. Spiller states that stretching or even cutting the external cutaneous nerve might be advisable if other measures fail. The nerve could be easily reached at the anterior-superior spine of the ilium.

F. Savary Pearce saw the same condition in a woman who had sepsis and had been subjected to operation upon the bladder and womb. In his case the middle cutaneous nerve of the thigh appeared to be alone involved.

Sailer has made the diagnosis in 2 other cases since his report on the subject.

Wharton Sinkler saw 2 cases of this disease. One patient was a woman who recovered several months later. The second case was a patient who suffered injury in a railroad collision. Intense burning pain was experienced in the distribution of the nerve.

McCarthy's case was a man, aged forty-eight years, who suffered for several years with an uncomfortable creeping sensation over the anterior and external surface of the right thigh. The left thigh also became affected. For nine years he had worn a heavy truss to control a bilateral inguinal hernia. There was anesthesia to the strongest faradic current and changes in temperature and touch sensation, and there were vague, uncomfortable paresthetic sensations over the antero-external surfaces of the thighs, extending to a few inches above the patella. F. X. Dercum believes that these cases are not uncommon and that the condition is a neuralgia of the external cutaneous nerve of the thigh.

Chipault has operated on 3 cases with great improvement of the symptoms. As this nerve is only sensory, resection would only cause loss of sensation in the part supplied by it. Mauclaire and Wondsbeck also obtained excellent results from resection of the nerve.

Gordon (1900) in his report states about 100 cases have been reported since Roth's and Bernhardt's papers in 1895. Gordon's patient was a neurasthenic man, aged forty-five years, who had typhoid fever four years previously. He began to suffer intense pain in the region of the fourth sternocostal articulation during convalescence. At the same time pain appeared in the antero-external and posterior surface of the left thigh. The pain was present for two years. He complains of a burning sensation over the antero-external surface of the upper two-thirds of the thigh from the anterior-superior spine of the ilium down and over the posterior surface of the upper third, from the crest of the ilium down, covering the external surface of the buttock. The tactile sensation is much diminished. When he walks the burning sensation is associated with pain, the pain appearing after he has walked for a few minutes. Pinching and rubbing are extremely painful. The thermic sensa-

tions are normal. In Gordon's case intermittent lameness (Charcot-Goldflam) was present; this is usually due to some constriction or obliteration of the arteries of the affected limb when it occurs in aged people. Several nerves, including the posterior branch, as well as the anterior branch of the external cutaneous nerve, and the cutaneous branches of the crural nerve were involved in Gordon's case. He concludes with a discussion of the atypical features of his case and a consideration of the etiological factors. Potassium iodide and massage seemed to help, although he insists that excision of the external cutaneous nerve is the only treatment for a case of genuine meralgia paresthetica.

Price's case (1909) occurred in a white married woman, aged thirty-one years. Her symptoms began when she was two months pregnant. She complained of sharp or cramp-like pain occasionally on the outer surface of the thigh, with paresthesias over the same area, particularly "numbness." There was some tenderness on pressure. The pain was made worse by walking and at times the pressure from the clothing caused discomfort. There was loss of pain sense and diminution of tactile and temperature sense. He treated her with hot fomentations locally, aspirin internally, rest, galvanism—resulting in prompt improvement. When she again became pregnant the trouble returned. At four months she miscarried and the paresthetic symptoms again disappeared under treatment. She had several miscarriages, but Price does not mention whether syphilis was present or not.

White's (1906) patient was a man, aged fifty-five years. He complained of tingling of the outer lower two-thirds of the right thigh; there was a dull, deep pain or ache at times. These sensations ceased on sitting or lying down. The middle cutaneous nerve was not involved in his case.

H. C. Baum and H. Goldenberg, physicians, suffered from this disease. Baum (1906) said he personally suffered from this condition for eleven years. He had seen 2 other cases exactly like his. He complained of a perverted sensation; sometimes there was formication, or prickling, or a sensation of heat or intense cold; there was no anesthesia. He always felt worse when fatigued or ill of any concurrence.

Hyde thought hypertrophy of the prostate might be a factor in some cases.

Hirsch's (1896) case was a man, aged fifty years, who had had syphilis eighteen years ago, and indulged in alcohol liberally. This man was exposed after a shipwreck and a considerable weight had been borne by one leg for about an hour. The man complained of a "burning cold." He was free of these sensations at night or while reclining or sitting. There was no change in the electrical reaction and some diminution of thermal sense was present.

Conclusions. 1. Six cases of Roth's or Bernhardt's meralgia paresthetica are reported in this paper—two woman, two men, and two young boys.

2. There are probably 135 cases of this interesting affection recorded in the entire literature.

3. The etiology is not settled. Infection, strain and persistent continued slight trauma have some bearing and influence on the appearance of this condition.

4. Treatment depends on the cause, if that can be discovered. Rest and avoidance of the usual occupation that traumatizes the front and side of the thighs, excessive walking, jumping or continued standing should be avoided.

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CHRONIC TUBERCULOSIS OF THE KIDNEY.[1]

By Edwin Beer, M.D.,
NEW YORK CITY.

This subject was selected for my paper of the evening because it seemed to me that it would make an appeal to a general audience. I welcomed the opportunity to present a review of this subject to you, as my experience has shown me that the profession does not fully appreciate the clinical picture of renal tuberculosis and the great importance of its earliest recognition, when still localized to one kidney. Before an audience of this character I naturally shall not go in great detail into many of the refinements in diagnosis and treatment that have developed in recent years, and even if I fail to tell you anything particularly new, I feel sure I shall have reawakened your interest in the subject under discussion and perhaps helped you to recognize cases of this disease.

There has been a growing tendency to call experts to make the diagnoses when the patient's symptoms fail to respond to treatment, and ultimate reliance on the expert has undoubtedly interfered with the general practitioner's independent and early recognition of renal tuberculosis. One can readily understand the practitioners' attitude, based as it is on their unwillingness to admit their inability to treat such slight symptoms as most patients present in the early stages of renal tuberculosis. But in fairness to the patients, why do they persist so long in blind treatment of these cases without arriving at a definite diagnosis? In the typical cases the expert should not be required to make the diagnosis, but his work becomes absolutely necessary in deciding which kidney, or whether both are diseased or not.

There is probably no disease which surgery has done more to clarify in every detail than renal tuberculosis. Its pathology, its diagnosis and its treatment have all been placed on a firm foundation by the surgeons; and as it is unfortunately a very frequent renal disease, in fact the most frequent renal disease that requires removal of a kidney, surgery can be proud of its accomplishment. Many of the profession in all lands have contributed to this study. I need mention only such names as Gross, Steinthal, Morris, Guyon, Tuffier, Israel and Brown to emphasize the international coöperation that has helped to clarify our views on chronic renal tuberculosis.

The view that chronic tuberculosis of the kidney usually began as a unilateral affection secondary to some other often inactive focus only gradually gained acceptance. Pathologists who saw the

[1] A Clinical Lecture delivered before the Wayne County Medical Society, Detroit, Mich., January 17, 1921.

end-picture of this disease, with tuberculous deposits in both kidneys, in the ureters, in the bladder, perhaps also deposits in the prostate, vesicles, epididymes, not to mention more distant foci in the lungs, meninges, joints, bones, etc., were slow to accept the new teachings, based on surgical experience and a few small series of autopsies. Now it has become our daily experience that these kidney deposits are the only active disease, and if a nephrectomy is performed the patient is cured and rid of his active tuberculosis. This marvelous change in the conception of the pathology of chronic renal tuberculosis in contradistinction to acute and subacute miliary tuberculosis is based entirely on surgical experience of the last forty years, and more especially on the work of the last twenty years. With this change in the conception of the disease the importance of early diagnosis became all the greater, and nowadays, with the aid of the cystoscope and the laboratory, suspicious cases are carefully investigated, so that the surgeon is seeing more and more patients in the early stages of renal tuberculosis than ever before. Still even at this date many patients suffer for months before their condition is realized. In going over a series of well over 100 cases I find that nine to twelve months have elapsed from the beginning of the typical symptom-complex until the real condition was definitely diagnosed.

Though chronic renal tuberculosis occurs at all ages it is most common in the third and fourth decades, that is between the twentieth and the fortieth year. It is much less common before the twentieth and after the fiftieth years, though we have seen a number of cases in young children and at least 10 cases in patients over the fiftieth year. This agrees fairly well with other large series that have been published except in the slightly greater frequency after the fiftieth year.

As far as sex is concerned males have slightly outnumbered females. In this regard American data seem to vary from those of our European colleagues. Braasch finds males 63½ per cent to 36½ per cent females afflicted with this disease, whereas Wildbolz[2] quoting the figures of European writers, says males are less frequently affected than females in the ratio 1 to 2. If the autopsy data are taken as criteria, rather than the operative data, it would seem that even in Europe the male is more frequently afflicted than the female. The diagnosis formerly was made more readily in the female, and perhaps that accounts for the contradiction between the published incidence in the two sexes. Of the cases that come to operation the right kidney is more often involved that the left, possibly because of its greater mobility. Unfortunately at least 10 per cent of cases come to us when both kidneys are involved in tuberculous disease and at a stage when no radical procedures are

[2] Chirurgie d. Nieren tuberkulose, 1913.

justifiable. In this our experience agrees fairly well with published reports (11 per cent to 14 per cent).

To grasp the symptomatology of chronic tuberculosis of the kidney it is essential to understand the main pathological features of this disease. Practically all cases are hematogenous in origin, being secondary deposits through the blood stream. Very rarely is the involvement ascending and only (in my experience) secondary to prostatic tuberculosis which has led to involvement of the bladder, dilatation of the ureters, followed by ureteral tuberculosis, tuberculosis of the pelvis and kidney or kidneys, the disease being less advanced in the upper urinary tract than lower down. In a large series of cases occasionally one sees a beautiful demonstration of the hematogenous deposit limited to one pole of a kidney, through an accessory artery to which Israel called attention years ago.

For many years there has been considerable dispute as to the primary renal focus, but gradually as surgeons are recovering specimens of earlier and earlier disease it has become more and more evident that in the majority of cases the first manifestation of the disease is in one of the papillæ of the kidney. Whether it starts near the base of the papilla or near its tip cannot be determined, though it would appear that both are favorite sites for the deposit of the tubercle bacillus. Kuester, Oraison, Rovsing, Wildbolz (Wildbolz, p. 26)[3] as well as we have very rarely seen a tuberculosis of the pelvis as primary deposit (L. Buergers[4] case. L. S.). Twenty years ago this was not accepted by investigators, because at that time more advanced cases, cases with extensive caseation, were being operated upon. As the papillary involvement progresses there is extension both into the cortex and into the calices and main pelvis. The bacilli appear to break into the vascular channels as they produce necrosis and caseation, and are carried toward the cortex producing tubercles, and discrete abscesses which both are often found directly under the capsule or separated therefrom by a thin layer of degenerated parenchyma. These shut off depots in the parenchyma of the kidney which do not communicate with the pelvis, probably rarely give symptoms until they perforate into the pelvis or into the perinephric space, which latter is a rare occurrence.

On the other hand the important extension of the papillary tuberculosis is toward the calices, the pelvis, the ureter and the bladder, and in these cases we get the typical symptoms of the disease. Ulcers and tubercles develop in the calices and the pelvis, as well as in the ureter, especially in its upper and lower ends, and finally the bladder is involved in the tuberculous process. With the inflammatory changes in the pelvis, the ureter and the bladder, thickening of the walls of these organs takes place and not infrequently stricture formation with obstruction to the outlet of the kidney secretion.

[3] v. ante.

[4] L. Buerger.

Not infrequently one sees reparative processes in these tuberculous kidneys, as evidenced by extensive scar formation in a calyx which has shut off an abscess or a tuberculous cyst either near the base of a papilla or in the cortex of the kidney, after destruction of a papilla.

In other cases the caseation has gone so far that little or no parenchyma is left and only a pultaceous or partly calcified mass, more or less of kidney shape, persists. If the stricture formation in the ureter is marked, pyonephroses develop, occasionally though rarely only a hydronephrosis. If secondary infection is superadded we see all the changes associated with acute or chronic pyelonephritis added to the picture of renal tuberculosis; occasionally even calculi complicate the picture.

As the process in the parenchyma progresses the perinephric tissues almost regularly undergo inflammatory changes, with or without miliary abscess formation and absorption of perinephric fat. At times a massive perinephritis develops which envelops the kidney in a shell of inflammatory tissue of great density and 1 cm. or more in thickness.

It is evident from this superficial sketch of the pathology that two processes appear to be going on side by side, destruction and protective repair, similar to what is seen in tuberculous disease in other organs. Unfortunately, however, the destructive processes regularly gain the upper hand, and though kidneys are occasionally seen in which extensive calcification or hydronephroses with complete parenchymal absorption have resulted, or empty shells of kidneys which may have discharged their caseated parenchyma through rigid open ureters. these abortive attempts at Nature's cure are so rare that one cannot expect in any given case even such a measure of success from a waiting policy.

As the tuberculous process in the kidney begins usually in the papillary zone the patients generally present a rather uniform symptom-complex which possibly varies with the natural immunity of the patient, expressed in his or her reparative processes as just outlined. No matter what the termination of the disease, whether it end in hydronephrosis, pyonephrosis, stricture of the ureter, perinephritis with abscess, secondary pyelonephritis (non-tuberculous or not), I am under the impression that a careful search of the history will present almost always a rather uniform picture of shorter or longer duration, which is so clear-cut as to be almost diagnostic. When we compare the value of the patient's history of his troubles in gastric or duodenal ulcer with that of the history in the cases under discussion, I am inclined to the opinion that renal tuberculosis gives a more definitely diagnostic train of symptoms than ulcers in the above-mentioned organs.

The striking symptoms of the typical cases are:

1. Frequency (and urgency) of urination.
2. Pain on urination.

3. (*a*) Pyuria (albuminuria).
4. (*b*) Hematuria. Pain in the lumbar region.

These symptoms usually develop insidiously, gradually increasing in severity. Occasionally, however, their development is very sudden—out of a clear sky, as it were, (described later on.)

1. Almost all patients complain of frequency of urination shortly after the beginning of the disease, and though there are occasionally periods of remission, the old symptom recurs to annoy the patient. As these cases often excrete an increased amount of urine their frequency is due in a measure to the polyuria in greater measure, however, to the local irritation of the disease. This annoying frequency may become so marked and the bladder control so impaired that a condition of pseudo-incontinence results. In fact, several cases that have come to us in the young had been under treatment for long periods as cases of enuresis (both night and day). This frequency may be so marked (every ten to fifteen minutes) as to prevent sleep, and as it is usually associated with marked urgency and pain the patients may suffer absolute torture.

2. The character of the pain on urination as well as its location seems to vary. Many patients complain of a burning or pricking sensation either in the deep urethra or near the meatus; others again have localized the pain at the neck of the bladder. In some the pain may be most marked as the bladder is emptied, when they become excruciating, often bringing tears to the patient's eyes. Anodynes are often required in these cases.

3 (*a*) Pyuria is an early symptom and the freshly voided urine with its finely distributed flocculi of pus cells produces an almost characteristic looking, delicate cloudiness. Whether absolutely clear, brilliant urine, as has been repeatedly declared, can be recovered in cases with involvement of the papillæ or pelvis I doubt, though it can readily be seen that such specimen might readily be voided when the process is not in free communication with the excretory channels. It cannot be emphasized too often that it is only when the tuberculous process extends into the excretory channels that the characteristic symptoms develop. In fact, one often sees extensive renal tuberculosis shut off in the parenchyma which has produced only transient symptoms of bladder irritability, succeeded by apparent perfect health, only to suddenly flare up as a fresh extension into the excretory channels develops with the production of symptoms of violent vesical involvement. In the literature a remarkable stress has been placed on the presence of a premonitory albuminuria. Albuminuria is regularly present when there is a pyuria and its significance is far outweighed by the recognition of the pyuria. Whether a really "premonitory albuminuria exists prior to the pyuria, that is prior to the extension of the disease into the excretory channels, I have not been able to convince myself. Still, it must be admitted that at this stage of the disease such an

albuminuria is easily understandable and all mild persistent and unexplained cases of albuminuria should be regarded with some suspicion.

3 (*b*). Hematuria varies greatly in these cases. There frequently is a slight admixture of blood in the purulent urine and well mixed with the same. Other cases pass a few drops or a small amount of fresh blood at the end of micturition as their bladders contract. Severe renal hematuria, as the first symptom in the disease, is an infrequent occurrence in our cases.

4. Pain in the kidney region, at times radiating along the ureter, has been much less frequently noted in our series than in the earlier published series. Some authors (Wildbolz, etc.) believe that pain in the kidney region antedates the symptoms of cystitis in 43 per cent of cases. In looking over the records of the more intelligent patients it is quite surprising how regularly they failed to refer any of their symptoms to the kidney region at the stage in which the bladder symptoms were their chief complaint.

It is remarkable how regularly case after case of renal tuberculosis complains of these characteristic symptoms and without any extensive questioning describe the above picture of bladder irritation, cloudy urine, perhaps hematuria, perhaps pain in the kidney region. They almost invariably report months of local treatment with no effect, though occasionally slight temporary improvement has been noted, only to relapse into a condition of greater distress than existed before the period of apparent improvement. While these are the typical cases, and while their history should suggest the correct diagnosis, which can be confirmed by the proper urinary examinations, there are numerous atypical cases, most of which undoubtedly commence in the above way and then gradually become quiescent or masked, while others, which is unusual, apparently fail to notice the usual symptoms of bladder irritation or by the time they seek medical aid have forgotten that period of their trouble.

These atypical cases are much more difficult to recognize and often baffle an expert urologist for some time. Some of these cases start as a massive hematuria, with or without ureter colics as the very first symptom, and this may rarely be so severe as to require transfusion and even nephrectomy. On the other hand the severe bleeding may cease and then the regular picture of the typical cases may develop.

In some cases the reparative and thickening processes, especially if they occur in the ureter, exclude the disease from the excretory passages, and after a brief period of vesical irritation all the symptoms cease as either a pyonephrosis or a hydronephrosis develops above the closed-off ureter. If the process becomes closed off by stricture formation at one or more calices a similar cessation of symptoms may ensue, but sooner or later as the disease recrudesces

a rupture or an extension into the pelvis takes place and suddenly all the symptoms of the typical cases are in evidence. In still another type where a mixed infection has developed the symptoms of the superadded infection, whether it be Bacillus coli or not, may so dominate the picture that one does not even suspect the diagnosis of tuberculosis until the kidney has been removed.

The same applies to some of the cases in which stone complicates the chronic tuberculosis. Another, a fourth, atypical development is that associated with perinephritis, especially the hyperplastic and suppurative types of perinephritis. Fortunately these are unusual and the diagnosis may not be made until some of the perinephric tissue is placed under the microscope. In all of these atypical cases except those with massive bleeding as the initial symptom one is more liable to feel a kidney tumor than in the typical cases.

Having the history of a typical case, or of a case that has once had symptoms suggestive of renal tuberculosis, the first step in confirming the diagnosis is the search for tubercle bacilli in the catheterized urine. From our experience there is no doubt that in the majority of cases of pyuria due to tuberculosis the tubercle bacilli can be found, if careful and repeated search of the properly stained sediment is made. In very advanced cases with thick purulent urine the tubercle bacilli may be so few and far between that they cannot be found. The literature abounds in papers dealing with the difficulties offered by the presence of the smegma bacillus, but in our experience we have had no trouble in recognizing the typical grouped tubercle bacilli and have not confounded it with the smegma bacillus, which is so rarely if ever seen in the catheterized bladder specimen. In our experience over 70 per cent of the cases showed the bacillus of Koch, and if repeated search had been made the percentage would have been much higher. With the development of cystoscopic interpretation one often makes a definite diagnosis before the search is completed, and in these cases, the kidney having been removed for tuberculosis, further study of the urinary sediment is of no great value and consequently abandoned. In those cases in which the kidney has been excluded (autonephrectomy), or in which urine is brilliant and clear, the inoculation of a guinea-pig may at times recognize the tuberculous character of the process. It must, however, be remembered that a positive guinea-pig reaction is at times missed in cases of renal tuberculosis, and at other times this test is positive when the patients have a tuberculous lesion in other organs. A careful analysis of the significance of tubercle bacilluria is always necessary [5] On the whole a positive smear is, in our experience, of greater value than a positive guinea-pig test.

[5] Beer, E.: Significance of Ureteral Tubercle Bacilluria. Am. Jour. Med. Sc., August, 1917, vol. cliv.

Another very helpful point in the diagnosis is the culture of the catheterized bladder specimen in cases of pyuria. As the output of tubercle bacilli may vary from specimen to specimen it is always advisable to culture the urine. A sterile pyuria with acid urine is common in renal tuberculosis, whereas in all other conditions, except perhaps in nephrolithiasis, it is rarely seen.

Whereas the above data when positive practically invariably mean urinary kidney tuberculosis in the female, it must not be forgotten that in the male prostatic tuberculosis may rarely produce a picture closely simulating that of typical cases of renal tuberculosis and tubercle bacilli may be present in the urine. Even an expert may find difficulty in interpreting the findings in such a case.

It will surely be conceded that patients whose symptoms suggest the presence of a renal tuberculosis should have their cases studied in this way, and so far by the general practitioner. Having made the diagnosis of tuberculosis in the urinary tract the need of a urologist of experience becomes evident. Some of these cases, in fact too many, are referred without the above studies to the general surgeon who has had no experience in urological diagnosis, a development of the last twenty-five years, and if there is local tenderness and perhaps a palpable mass in the kidney region, such a case is operated upon forthwith, either a nephrectomy or a nephrotomy being done. To operate on any kidney case without attempting to determine the presence of an adequate second kidney prior to the operation is nowadays absolutely unpardonable. All these cases should be studied carefully by the cystoscopist, who must determine, using gas-oxygen anesthesia if necessary where the disease is, and if in one kidney whether the second is healthy and adequate. It is up to the cystoscopist to rule out prostatic tuberculosis as a source of the tubercle bacilluria and it is up to him to diagnose the exact condition of the diseased kidney and to determine that the second organ is not tuberculous.

Fortunately all these things can be done with great accuracy. Experience has proved conclusively that the lesions in the bladder, the edematous ureteral meatus, its more or less rigid walls, the adjacent polypoid (or pseudopapillomatous) edema, its retraction as the ureter becomes thickened, the ulcers and the tubercles about the involved ureter produce a picture which is sufficiently characteristic to make the diagnosis. In 1907 Rovsing[6] made the statement that occasionally the bladder involvement is about the ureter meatus of the healthy kidney. Personally in hundreds of cases examined by me this has never obtained. In view, however, of this publication it is advisable to collect ureteral specimens whenever possible and confirm the presence of pyuria and tubercle bacilli on the side that is chiefly involved in the bladder disease. The use of indigo carmine is invaluable in this work, not only as an aid in

[6] Arch. f. Klin. Chirurg., 1907, lxxxii, 10.

locating the ureters in diseased, contracted bladders, but also as an index of the relative function of the two kidneys; usually the diseased kidney excretes a less concentrated stream of indigo than its healthy fellow. In the strictured ureter cases it may be impossible to collect a specimen on that side and by exclusion of the other kidney whose urine is normal plus the local findings one decides that the tuberculosis is on the strictured side. On many of these cases careful observation will detect a weak little bluish stream trickling out of such a strictured ureter.

Before this audience it is scarcely advisable to go into extensive details concerning the cystoscopic picture in these cases. There is, however, one misconception that should be corrected. It is generally thought that the urine laden with bacilli infects the mucosa of the bladder and produces ulcerations which lead to exudation. This is highly doubtful. It is more likely a lymphatic submucous involvement with production of tubercles, and these gradually break down into ulcers. I have excised such tubercles from the lips of a ureter meatus and weeks later prior to nephrectomy found the excised areas smoothly covered with healthy mucous membrane, which would hardly have happened if the urine infected the mucosal surface as usually thought.

In the typical cases the specialist will be able to clarify the clinical picture and confirm the diagnosis. Rarely he will have to resort to other aids than those already mentioned, such as the roentgen ray of the urinary tract which in advanced cases may show very definitely, irregularly thickened or calcified areas in the kidney region. Pyelography, I believe, is contraindicated and unnecessary in these cases. It is still a moot question whether diagnostic doses of old tuberculin should be used in particularly obscure cases. There is no doubt that indiscriminate use of tuberculin may harm. On my service it is used only as the last resort prior to operation and occasionally has given valuable information both by increasing the output of bacilli, which had not been found prior to the injection of tuberculin, and by producing a focal reaction in the diseased organ accompanied by fever. With the general improvement in cystoscopic and laboratory work the use of tuberculin has become less and less frequent, and in the future it will be used exceptionally.[7]

Despite the most careful preoperative study one occasionally is in doubt as to whether one is dealing with a renal tuberculosis, and as the operative indication in this disease is a nephrectomy, one must confirm the diagnosis on the operating table. Today many of these cases come to the operating table at a stage when the microscopic external appearance of the kidney is that of a normal organ. If the ureter is thickened it is highly suggestive in a case of sterile renal pyuria with negative roentgen ray, that one is dealing with a tuber-

[7] Beer, E.: Use of Tuberculin in the Diagnosis of Obscure Conditions in the Genito-urinary System, New York Med. Record, October 11, 1913.

culous kidney, the history having been typical. Still before removing such an organ it may be necessary to do a nephrotomy and prove the presence of a tuberculous lesion (and exclude a uric acid calculus). Again, in some particularly difficult cases it may be necessary to expose both kidneys and by palpation of the ureter and examination of both kidneys decide which is diseased or whether both are diseased. With experience in cystoscopic work it is becoming less and less necessary to make the diagnosis on the operating table under either one of the above conditions. In recent years careful preoperative study has invariably sufficed to clarify the diagnosis.

Treatment. As renal tuberculosis may be part of a more general tuberculosis, before advising the only treatment that is of avail, namely, nephrectomy, it is essential to make a most thorough examination of the patient. Patients with pulmonary tuberculosis should be operated upon under gas-oxygen. If the disease in the chest is advanced and active operation is inadvisable. The same anesthesia should be used in decrepit or weakened patients. Spinal anesthesia will probably meet the same indications. I have used it successfully in this type of case.

In about 10 per cent of our cases the disease of the ureter has been very extensive producing strictures, in these the aseptic nephroureterectomy described recently[8] was rather regularly done. It is very striking to see how all the irritative symptoms cease directly after the operation and how the urine becomes clear at once. In the other 90 per cent we do a typical nephrectomy—remove a few inches of ureter, carbolize the stump, drop it back and close the wound with a tube drain. No great advantage has been seen from filling the wound with saline and closing it completely. In a series of 100 cases in which nephrectomy was done the mortality has been 2 per cent, and but for an error in interpretation it might well have been half of that. Evidently the operative risk is not serious.

Many series of end-results have been published. Braasch's[9] monumental work is the most recent publication of a large series from the Rochester Clinic, and it deserves careful study. His data show complete cure in 60 per cent; recovery 80 per cent; *i. e.*, deaths within five years of operation, 20 per cent. This corresponds fairly well with the experience of others. Patients who can take care of themselves have a better chance than the laboring classes. About 70 per cent of the former seem to be definitely cured and perhaps 50 to 55 per cent of the less fortunately placed. It is more than likely that with earlier recognition of this disease earlier operation will give even better end-results. If we turn to the end-results of non-operated cases as presented to the German Urological Society

[8] Beer, E., and Hyman, A.: Progress in Nephrectomy, Jour. Am. Med. Assn., October 30, 1920, vol. lxxv.

[9] Surgical Renal Tuberculosis: The Prognosis, Am. Jour. Med. Sc., January, 1920. Verhandl. d. Deutschen Gesellschaft f. Urologie, 1912.

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by Wildbolz (p. 108) we find that in 316 non-operated cases only 20 per cent lived longer than five years.[10]

Such data teach very definitely that a tuberculous kidney should be removed as soon as the diagnosis is made and while the disease is still unilateral. Today in close to 10 per cent of the cases when first examined the disease involves both kidneys, pus and tubercle bacilli being definitely found in the secretion of each organ. If nephrectomy of the more diseased organ is done I have never seen any real gain to the patient, and it is my belief that the cases in which marked improvement has been reported may not have been bilateral renal tuberculosis. In a paper on the significance of ureteral tubercle bacilluria.[11] I have called attention to some of the factors which may underly a mistaken diagnosis of bilateral tuberculous disease when the disease is unilateral. Moreover, when both organs are definitely diseased it may be difficult to decide which one is causing more trouble and which one is more diseased.

Functional tests will not regularly help in making this distinction. If one organ delivers practically pure pus and little urea, and is, moreover, a useless sac producing disturbance, its removal may benefit the patient even though the second kidney be diseased and its tuberculosis be uninfluenced. Braasch reports 13 deaths within one and a half years following nephrectomy in 16 patients with bilateral disease, and in a series of 62 cases Israel found that about 70 per cent had died shortly after the nephrectomy.

After the removal of the kidney in unilateral involvement the patient unfortunately is not cured and well. There is always some tuberculosis left in the urinary tract which Nature usually takes care of, provided the patient leads a well-regulated existence. The general hygiene of these patients must be supervised and their resistance carefully built up by nutritous diet and fresh air.

Another difficulty which these patients present is the formation of a sinus (in at least 10 per cent of cases) in the lumbar wound which may take months to heal. These sinuses seem to develop in a definite number of cases even though the operation has been absolutely aseptic and no tuberculosis material has been split. These sinuses are usually spoken of as ureter sinuses, but I believe this is a misnomer, as I have seen them repeatedly even when the ureter and kidney have been removed in one piece. At times the whole lumbar wound breaks down with tuberculosis some five or six weeks after the nephrectomy, and then has to be laid wide open. My experience has suggested to me that we are dealing in these slow-healing postoperative wounds with a tuberculosis due to a tubercle bacteremia induced by the operative manipulations. Attempts to pick up the tubercle bacillus in the circulation during the operation have, however, regularly failed despite the use of guinea-pigs. Improved or modified technic will probably be more successful.

[10] Wildbolz: Ibid.

[11] Vide ante.

Another condition that may seriously trouble these patients after nephrectomy is the persistence of bladder symptoms with or without hematuria. Fortunately these symptoms gradually disappear in the majority of cases, but in others they plague the patient and they can see no benefit following the operation. All sorts of remedies have been suggested for these cases from Rovsing's carbolic acid to Marion's lactic acid bacillus milk injections. Personally I have seen the best results when using sandalwood oil and cystoscopic high-frequency cauterization of the usually extensive bladder ulcers.

Before closing this brief and rather superficial review of the most striking features of chronic renal tuberculosis, I must say a word about the complications that develop in other organs in those patients that die either after the operation or unoperated. Experience has shown that after nephrectomy those patients who are destined to die develop complications usually within a year of the operation and die as a result of these complications. Whether the dormant processes in other viscera are activated by the operative procedure or whether the operative trauma produces a bacillemia has not been proved. Both factors probably play a part. The frequency of a subacute miliary tuberculosis following the operation, in the 20 per cent that do not live longer than two years must be borne in mind. We have seen several cases of tuberculous meningitis within a few months of the nephrectomy, but as autopsies were not performed it was not known whether this was part of a miliary tuberculosis or not. Careful studies have shown that pulmonary tuberculosis, tuberculosis of the second kidney often unrecognized at the time of operation and miliary tuberculosis contribute to the death-toll during the first and second years following the nephrectomy. In those cases of renal tuberculosis which for one reason or another did not come to operation, the data at hand suggest that renal insufficiency, general amyloid disease due to chronic suppuration and pulmonary tuberculosis lead to the fatal issue. Miliary tuberculosis seems to play less of a role than in the postoperative cases. This naturally leads to the conclusion that in doing a nephrectomy one should traumatize as little as possible, so as to avoid driving bacilli into the circulation.

If during the next generation the developments in the surgery of renal tuberculosis progress as remarkably as they have during the past twenty years, patients will regularly come to the operating table in the earliest stages of their trouble and their chances of permanent relief will thereby be markedly improved. As we have seen the operative risk is low, and the mortality during the first years after the operation is still much too high. Earlier diagnosis and earlier operation followed by better postoperative care will surely lead to better end-results, and with generous coöperation we look forward to a future accomplishment of which we all shall be proud.

REVIEWS

PRINCIPLES OF BACTERIOLOGY. By A. C. ABBOTT, M.D. Professor of Hygiene and Bacteriology, and Director of the School of Hygiene and Public Health, University of Pennsylvania. Tenth edition, thoroughly revised, with 121 illustrations, 31 of which are colored. Philadelphia and New York: Lea & Febiger, 1921.

A NEW edition of this well known and useful handbook of bacteriology needs but little comment in this journal. But few changes have been made since the ninth edition. Fuller consideration of the hydrogen-ion concentration of media and the Spirochetaceæ are the two chief additions, together with several pleasing pictures of the Pathfinders of Bacteriology.

E. B. K.

DISEASES OF THE SKIN. By OLIVER S. ORMSBY, M.D., Professor and Head of the Department of Skin and Venereal Diseases, Rush Medical College (in affiliation with the University of Chicago); Dermatologist to the Presbyterian, Saint Anthony's and West Suburban Hospitals, and the Home for Destitute Crippled Children; Consulting Dermatologist to the Orphan Asylum of the City of Chicago; Member of the American Dermatological Association and of the Congress of American Physicians and Surgeons; Corresponding Member of the Section of Dermatology of the Royal Society of Medicine, London. Second edition. Pp. 1166; 445 engravings and 4 plates in color and monochrome. Philadelphia and New York: Lea & Febiger, 1921.

DR. ORMSBY has made a thorough and complete revision of his book, *Diseases of the Skin*. Although four hundred pages have been rewritten and fifteen new diseases described, the size of the volume remains the same. This has been accomplished by the elimination of everything superfluous and by concise description. The excellence has been maintained throughout.

The classification has been amplified notwithstanding the number of chapters remains the same. MacKee's dosage and a chart descriptive of his method have been added. Many important references have been included enhancing the value of the work to those desiring research.

Numerous engravings and monochromes have been removed to make room for those more practical and artistic. The present volume contains one hundred and forty-two more engravings than the former.

The advances in syphilis are fully recorded. Among the new diseases described are the following: Keratolysis exfoliativa; folliculitis ulerythematosa reticulata; vaselinomata; chondrodermatitis nodularis chronica helicis; precancerous dermatoses; nocardiosis cutis; Vincent's disease; periadenitis mucosa necrotica recurrens; atrophy of the mucous membrane of the tongue and mouth.

Dr. Ormsby is to be congratulated on the excellence of his work.

F. C. K.

TUBERCULOSIS AND HOW TO COMBAT IT. By FRANCIS M. POTTENGER, A.M., M.D., LL.D., F.A.C.P. Pp. 273. St. Louis: C. V. Mosby Co., 1921.

THIS book is written for the patient, not for the physician. There are few books of worth published for the guidance of the patient save on two subjects—diabetes and tuberculosis. In these essentially chronic conditions the possibility of success in treatment depends upon the patient himself.

Dr. Pottenger's little volume consists of a summary of his talks with his patients. The chapters are brief, each taking up a single proposition or very limited phase of the subject which is discussed without rambling or deviation. The book can thus be read chapter by chapter. The statements are clear and the style concise throughout. The tone is optimistic. The subject of treatment from the standpoint of the patient is thoroughly covered. Whether or not we agree with all of Dr. Potrnger's views as stated in these pages is beside the point. The book is well calculated to stimulate the efforts and encourage the perseverance of the intelligent patient.

R. G. T.

A PHYSICAL INTERPRETATION OF SHOCK, EXHAUSTION, AND RESTORATION. AN EXTENSION OF THE KINETIC THEORY. By GEORGE W. CRILE, M.D., Senior Consultant in Surgical Research, A. E. F., 1917–1918; Professor of Surgery, School of Medicine, Western Reserve University. Edited by Amy F. Rowland, B.S. Pp. 221; 120 illustrations. London: Henry Frowde, Hodder and Stoughton, 1921.

THIS volume presents a summarization of the many researches made by the author and his assistants in their laboratories and clinic at Cleveland, and of the author's observations and research in this subject during the war.

The introduction, in two parts, bears upon the methods of production of shock and exhaustion in the soldier, and upon the coexistence of clinical phenomena and histologic changes in various organs in exhaustion.

The mechanism of shock, exhaustion and restoration as elaborated by the author is dwelt upon in the summaries of the earlier monographs on these subjects, and in addition there are restated the principles upon which shockless operations may be performed.

Further, the author reviews the physical laws upon which he bases his theories, and develops his further researches upon the physico-chemical and electro-chemical considerations and interpretations of the mechanism of shock.

Certain clinical phenomena, as fever, exophthalmic goiter, inhalation anesthesia, tetanus and strychnine poisoning are interpreted theoretically in the light of the author's beliefs.

The practical application of the kinetic theory in treatment is extremely interesting, as to the observations, deductions and suggestions offered which may be put into clinical practice to the benefit of the patient.

The book is an excellent recapitulation of the well-known ideas of the author, and the addition of his observations on the battlefield adds an extra interest to the always intriguing subject of shock.

P. F. W.

FUNDAMENTALS OF BACTERIOLOGY. By CHARLES BRADFIELD MORREY, Professor of Bacteriology, Ohio State University. Second edition. 171 engravings, 6 plates. Philadelphia and New York: Lea & Febiger, 1921.

IN this edition the author supplements the first with the more recent developments in Bacteriology. He includes for discussion the system of classification as adopted by the American Society of Bacteriology, and their key to the genera of bacteria; the hydrogen-ion concentration method of standardization of media; selective action of aniline dyes; the mechanism of invasion of microörganisms into the body; the origin of antibodies; and the nature of antigens, with a table of antigens and antibodies.

The book is well written and clarifies some abstruse points which are ever stumbling blocks for the embryonic bacteriologist. The author's discussion of immunity and hydrogen-ion concentration particularly demonstrate this feature. In a clear and concise manner he has taken up the points just enumerated, and has brought his book as much abreast of the times as a text-book in a growing science can be. Many statements are followed by examples, which may add to their practicability and interest for the student. The discussions are brief, serving only as introduction to the study of

bacteriology. The book is a good primer, but should be followed with more detailed books for the advanced student.

A description of the individual bacteria is not included, constituting a new departure from the usual style of bacteriological text-books; so that in teaching the medical student, at least, it would not quite fill routine requirements. There is no detail in the book, which may favor the instructor by allowing him to expand on any topics which appear of more importance to him. In short, if brevity is the soul of wit, then the author has succeeded in putting before the bacteriologist, a clear, up-to-date text-book in the fundamentals of bacteriology. L. J.

SURGICAL CLINICS OF NORTH AMERICA. Vol. I, Nos. ii and iii, New York and Boston numbers. Illustrated. Philadelphia and London: W. B. Saunders Company, 1921.

THESE clinic reports are now an established publication and the Nos. i, ii and iii are respectively the work of Philadelphia, New York and Boston writers. Up to the present, at least, these new clinics are adhering to the real type of clinical reports, *i. e.*, with the elimination of all unnecessary routine data in a case report, which data has no bearing at all on the subject. In these numbers there seems but one real dereliction of this type.

The authors are all representative men in their subjects and their presentations are all worth careful scrutiny and study. There are thirty-four contributors in all to the two volumes, giving the reader excellent reading in a small, compact form that can be kept as a reference book. E. L. E.

ESSAYS ON SURGICAL SUBJECTS. By SIR BERKLEY MOYNIHAN, Leeds, England. Pp 253; illustrated. Philadelphia and London: W. B. Saunders Company, 1921.

THIS book consists of a number of essays or articles that have been written and published at various times during the last few years. They have been altered somewhat and the statistics brought to date. This collection of articles is justified in the eyes of the author in that thereby is presented a consecutive train of thought.

The works of the author need no recommendation. His style and diction are always the best, and one reads his sentences with at once an appreciation of the valuable facts presented as well as the charming style of their expression. It makes most pleasant and instructive reading. E. L. E.

MANUAL OF OPERATIVE SURGERY. By JOHN FAIRBAIRN BINNIE, M. D., Surgeon to the Christian Church, the Research and the General Hospitals, Kansas City. Eighth edition. Pp. 1311; 1628 illustrations. Philadelphia: P. Blakiston's Son & Company.

THE greatest changes in this new edition will be found in the chapters on Thoracic, Abdominal and Plastic Surgery, all of which have been practically rewritten. The chapter on Orthopedics has been thoroughly revised and most of the article on War Surgery has been omitted. This volume contains more material in a smaller number of pages than does the preceding edition.

The constant endeavor is to give aid and guidance to the surgeon when he is in trouble, putting emphasis on the unusual rather than on the common, as would a text-book. Hence the great space allotted to cardiac surgery, head surgery, retroperitoneal tumors, etc. The book is thoroughly up to date and complete in every respect. E. L. E.

LABORATORY MANUAL OF THE TECHNIC OF BASAL METABOLIC RATE DETERMINATIONS. By WALTER M. BOOTHBY, A.M., M.D., and IRENE SANDIFORD, PH.D., of the Mayo Clinic, Rochester, Minn. Pp. 117; 13 illustrations. Philadelphia: W. B. Saunders Company, 1920.

THE gasometer method of determining basal metabolic rate is herein presented very clearly and concisely. The book is more valuable to the laboratory worker in this line than to the clinician, who customarily uses the less complicated and sufficiently accurate methods based upon oxygen consumption. W. H. S.

TREATISE ON FRACTURES. By JOHN B. ROBERTS, M. D., Emeritus, Professor of Surgery in University of Pennsylvania Graduate School of Medicine, etc., and JAMES A. KELLY, M.D., Associate Professor of Surgery in University of Pennsylvania, Graduate School of Medicine, Surgeon to St. Joseph's, St. Mary's, St. Timothy's and the Misericordia Hospitals. Second edition. Pp. 755; 1081 illustrations. Philadelphia: J. B. Lippincott Company.

THE text of this second edition has been thoroughly revised to meet the needs that we know today govern the results in fractures. As an outcome of the war we have gained enormously in our knowledge of how to handle broken bones. The authors have fully appreciated these advances and show us in this work the latest ideas and the most modern treatment of fractures. A book of this type

is now absolutely essential for any man treating fractures. Workmen's compensation laws and the payment for all hospital accident cases have deepened the responsibility of the one caring for a fracture.

The numerous and excellent illustrations do more to present the subject properly than does the text unaided. The writers drive home the point that there is no fixed and dogmatic rule for fracture treatment unless it be that the surgeon have great adaptability, patience and constant supervision, for responsibility does not cease with the mere reduction of the fragments, for then come the most important features, namely, how to maintain the reduction and return the patient to activity with good function. E. L. E.

SURGERY OF THE UPPER ABDOMEN. By JOHN B. DEAVER, M.D., Professor of Surgery in the University of Pennsylvania; Surgeon-in-Chief to the Lankenau Hospital, and A. P. C. ASHHURST, M.D., Associate in Surgery in the University of Pennsylvania, Surgeon to the Episcopal Hospital. Second edition. Pp. 832; 207 illustrations. Philadelphia: P. Blakiston's Son & Company.

THE first edition of the work was published in two volumes and this, the second edition, has followed the same general plan. Many sections have been entirely rewritten, *e. g.*, Gastric Ulcer, Infantile Stenosis of the Pylorus, Causes of Death after Operation on the Stomach and Duodenum, Jejunal Ulcer, etc. New material has been added on Operative Technic, Transgastric Excision of Ulcers, Resection of the Descending Duodenum, Surgery of the Spleen, etc.

A great deal that was obsolete was omitted, as well as extensive bibliographical references and statistical tables have been condensed. Nearly 100 new drawings have been introduced and now in this book of slightly over 800 pages more material is presented than was formerly included in two volumes running almost to 1000 pages.

The work is an excellent one, as would be expected it from these two authors. E. L. E.

THE DIAGNOSIS AND TREATMENT OF INTUSSUSCEPTION. By CHARLES P. B. CLUBBE, L.R.C.P., M.R.C.S., Consulting Surgeon to the Royal Prince Alfred Hospital, Consulting Surgeon to the Coast Hospital, Sydney. Second edition. Pp. 88. London: Henry Frowde, 1921.

THIS small clinical review on intussusception, it can hardly be called a monograph, as it is not sufficiently complete, contains the

author's experience with this rather rare condition. It contains first a general description of the condition, followed by a discussion of the anatomy and etiology, succeeded by a description of the various varieties that are likely to occur. The diagnosis is also considered, but the greater part of the text deals with the treatment of the condition. The author, to a certain extent, uses intestinal irrigation and by quoting a few case reports he notes specifically the cure occasionally brought about by irrigation. He has operated upon 253 cases and his operative results seem to be very satisfactory.

J. H. M., Jr.

Aids to Chemistry. By William Partridge, F.I.C., Public Analyist of the County of Dorsit. Lecture in Chemistry, King's College, University of London. Pp. 280. New York: William Wood & Company.

This useful hand-book presents in concise form, many useful facts in inorganic and organic chemistry. There is, however, no practical consideration of the medical aspects of chemistry presented.

E. B. K.

Chemical Pathology. Being a Discussion of General Pathology from the Standpoint of the Chemical Processes Involved. By H. Gideon Wells, Ph.D., M.D., Professor of Pathology in the University of Chicago, and in the Rush Medical College, Chicago. Fourth edition, revised and reset. Pp. 695 Philadelphia and London: W. B. Saunders Company, 1920.

The need of a fourth edition of this book within two years of the third, points to the rapid growth both of scientific knowledge in this domain and of the recognition of its value to clinician and investigator. A new chapter on the "Chemistry of Growth and Repair" has been necessitated by the growing importance of deficiency diseases and a separate chapter on "Anaphylaxis and Allergy" provided. The many excellent features of previous editions, here generously reinforced with new material, require no further commendation in this Journal.

E. B. K.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

ROGER S. MORRIS, M.D.,

FREDERICK FORCHHEIMER PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO,

AND

THOMAS ORDWAY, M.D.,

DEAN OF UNION UNIVERSITY (MEDICAL DEPARTMENT), ALBANY, N. Y.

Influenza as a Factor in the Activation of Latent Tuberculosis.—The incidence of active tuberculosis of the lungs following influenza and influenza pneumonias has been the subject of a number of papers since the epidermics of 1918–1919, many of these concluding with the observation that influenza had no appreciable effects on pulmonary tuberculosis, or even stating that the tuberculous were less susceptible to acute epidemic influenza than normal individuals. BOISLINIERE (*American Review of Tuberc.*, 1920, iv, 534) as early as December, 1918, encountered active tuberculosis in a number of individuals who had been seized with influenza only a few weeks previously, and who, up to the onset of influenza, had never varied from their usual standard of health. These cases recalled observations made during the pandemics of 1889 and 1890 to the effect that lungs that did not clear up within eight to ten weeks after an attack of "la grippe" were in many cases actively tuberculous. A census of a group of institutions devoted to the case of the tuberculous brought out the facts that from 15 to 20 per cent of the new cases of pulmonary tuberculosis presenting themselves since the onset of the influenza epidemic in 1918 gave no history suggestive of a previous lung lesion, and that they had been caused by the influenza. Further, the census indicated that the incidence of pulmonary tuberculosis has increased to the same extent during that period, and from the same cause. As the pathological basis for increased incidence of tuberculosis of the lungs following influenza, the author cites the acute hyperemia, interstitial edema and serous exudate which

according to him accompany even uncomplicated cases as tending to break down the protective barriers of a dormant tuberculous lesion. He points out that this tendency is much more marked in the instance of influenza and influenzal pneumonias than it is in ordinary lobar and bronchopneumonias. A second factor is that of lowered resistance, based on the negative von Pirquet reaction found during and for some weeks after influenza, a condition likewise obtaining in measles. The author does not mention the possibility of increased susceptibility to primary infection as a factor in postinfluenzal tuberculosis.

Agglutination in Influenza.—UTHEIM (*Jour. Infect. Dis.*, 1920, xxvii, 460) studied the sera of patients with influenza as to whether the serum of the patient would agglutinate the influenza bacillus obtained from the same patient and whether agglutination would take place with heterologous strains. The antigen consisted of cultures isolated from the nose or throat and suspended in salt solution. After thorough shaking, a homogeneous emulsion was usually obtained, spontaneous clumping occurring in only one instance. Thirty strains were isolated from as many patients and tested with the serum from these patients during different stages of the disease. It was found that 11 gave a positive agglutination with their own bacilli, 6 in a dilution of 1 in 160, 4 in 1 in 60, and 1 in 1 in 20. With the exception of one strain, which gave an agglutination of 1 in 40 with 3 sera of other patients, no cross agglutination was encountered in any serum tested. The blood of 9 patients was examined during different stages of the disease; 8 showed a constantly negative result, while in 1 instance the agglutination became positive in a dilution of 1 in 80 in the convalescent stage. Three strains were isolated from the throat of 1 patient, only 1 of which gave agglutination with the patient's serum. Seven of the 11 which gave agglutination with the homologous strain occurred in uncomplicated influenza and 4 in influenza pneumonia. Of the remaining 19 negative cases, 10 had pneumonia.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK,

AND

CHARLES C. LIEB, M.D.,

ASSISTANT PROFESSOR OF PHARMACOLOGY, COLUMBIA UNIVERSITY.

The Use of a High Fat Diet in the Treatment of Diabetes Mellitus. Second Paper: Blood Sugar.—NEWBURGH and MARSH (*Arch. Int. Med.*, 1921, xxvii, 699) supplement a previous communication (*Arch. Int. Med.*, 1920, xxvi, 625) in which they reported briefly the

results of an investigation of the effects of a diet whose energy came largely from fat, to which was added sufficient protein to maintain nitrogen balance, and the minimal carbohydrate necessitated in making up a diet that a human being can eat over a long period of time. It was shown that with such a diet glycosuria was avoided in severe diabetics and that acidosis was not produced. The present paper presents the blood-sugar determinations in 45 cases treated by this method. All but 5 more or less promptly responded with a reduction of the blood sugar to within normal limits. Of the 5 which did not reach a desirably low percentage 2 were suffering from severe complicating diseases and 1 was suspected of not adhering to his diet.

Dermatitis and Allied Reactions Following the Arsenical Treatment of Syphilis.—A detailed review is given by MOORE and KEIDEL (*Arch. Int. Med.*, 1921, xxvii, 716) of 23 cases of dermatitis and allied reactions following arsenical treatment which have occurred during the last six years in the syphilis department and in the wards of the Johns Hopkins Hospital and in the private practice of the authors. Five of the 23 cases terminated fatally. From the evidence presented it appears that the lesions of syphilis and the duration of the disease exercise no modifying influence upon the dermatitis. Dosage, technic of administration, impurities in the drug and the type of chemotherapeutic arsenic compound can be excluded as etiological factors. Reactions of this group tend to appear early in the course of treatment. The lesions may be classified, on the basis of the constitutional manifestations and their importance, as mild or severe. In the mild group fall urticaria and erythematous and herpetic rashes. In the severe group are macular, maculo-papular and exfoliative rashes, itching and stomatitis. In some cases certain prodromal symptoms may be recognized; itching, mild or fleeting skin eruptions, prolonged fever or marked malaise. The occurrence of any of these during the use of arsenical products should lead to a suspension of treatment and a general survey of the patient. Urticaria is fairly common in association with the nitritoid crisis, is not accompanied by the more severe constitutional manifestations and does not contraindicate continuance of arsenical treatment. The authors call attention to characteristic alterations in the blood picture, which were present in 14 of the 16 cases studied. The changes consist, in general, of leukopenia, decrease in polymorphonuclear neutrophiles, eosinophilia, increase of the large mononuclear-transitional group and the appearance of many fragile cells. The complications of dermatitis exfoliativa, including acute nephritis, polyneuritis, jaundice, skin infection, bronchopneumonia and septicemia, are discussed. In considering the possible etiological factors in reactions of this group the authors cite Auer's recent work and agree that arsphenamine may lower the local threshold for an unknown antigen which in its turn causes an anaphylactic reaction, and thus may cause the deposit of arsenic in the structures where its toxic action is observed, notably in the bone-marrow and in the skin.

Fatal Chronic Nephritis in a Fourteen-year-old Girl with only One Kidney and a History of Scarlet Fever.—PEPPER and LUCKE (*Arch. Int. Med.*, 1921, xxvi, 661) report a careful clinicopathological study

of a fatal case of renal disease in a fourteen-year-old girl. She had pneumonia at the age of two, typhoid fever at the age of three, and mumps at the age of four. At the age of seven she suffered from an attack of scarlet fever, after which she was never strong. There was no history of kidney involvement or edema. She had occasional attacks of belching and vomiting, which were more severe during the past two months. Two months before admission she had an attack of marked blurring of vision and loss of power and sensation in her left arm and both legs, and some difficulty with speech and swallowing. These symptoms disappeared within two weeks. Two weeks before admission she had an attack diagnosed as "grippe." Her menses began at the age of twelve and were exceedingly free, later being associated with bleeding from the nose. The last period commenced nine days before admission and continued with excessive nose-bleed and bleeding from the gums until admission. The positive features of the physical examination included a urinous odor to the breath, evidence of recent bleeding from the nose, the lips and the gums. Blood-pressure 148,132. Urine, 1008; alb. ft. tr.; many red blood cells and white blood cells. Red blood count, 2,270,000. White blood count, 5200. Hemoglobin, 50 per cent. Platelets, 220,800. Blood-urea nitrogen, 210 mg. per 100 cc. Blood plasma, CO_2, 29 vols. per cent. Phenolsulphonephthalein test, –0 in two hours. During the next three days the blood plasma, CO_2, increased to 50 vols. per cent, but the blood-urea nitrogen rose to 228 mg. per 100 cc, and after a steady downward course she died four days after admission. Necropsy revealed early general arteriosclerosis; slight congestion and edema of the lungs; slight fibrosis of the spleen; submucus hemorrhages of the intestines; cloudy swelling of the liver; slight cardiac hypertrophy; aplasia of the left kidney and its ureter. The authors then give a detailed description of the gross and histopathological condition of the small right kidney: a combination of true chronic interstitial nephritis and chronic glomerulonephritis, showing also a remarkable degree of frustrated regeneration. They point out the striking similarity of their photographs to that used by Aschoff to illustrate "genuine" contracted kidney (true chronic interstitial nephritis). In the discussion the authors review the two types of nephritis which occur as complications of scarlatina, acute interstitial and acute glomerulonephritis, and point out the rarity of an opportunity to study the terminal stage of nephritis following scarlatina. They speak of the rarity of true chronic interstitial or glomerular nephritis before the age of twenty. The literature on true agenesis of the kidney is reviewed. The authors reach the tentative conclusion that this unusual picture was the result of the injurious action of scarlatina initiating a nephritis, which because of the inadequate and possibly anomalous kidney present, rapidly resulted in a condition analogous to chronic nephritis of adults.

Comparative Systolic Blood-pressure Readings in the Arm and Leg in Aortic Incompetence.—A careful study of 24 cases of aortic incompetence led WILLIAMSON (*British Med. Jour.*, May 21, 1921, p. 734) to doubt the generally accepted statement that a diagnostic sign of aortic insufficiency is the higher systolic arterial pressure in the leg compared to that in the arm when the patient is at rest and in the recumbent

position. The author found that though higher systolic readings in the leg than in the arm appear in the majority of cases of aortic incompetence, there is a large minority (25 per cent) in which they do not obtain. The difference in the readings is due, according to the author, not to aortic insufficiency but to commonly associated conditions of hypertonic contraction or hypertrophy of the muscular walls of the arteries with or without sclerotic changes. In any event the large majority of cases in which the arteries were thickened showed the difference, while in children in whom the arteries were not hypertrophied the phenomenon was relatively rare. The difference in pressures, therefore, is vascular, not cardiac in origin.

The Control of Hemorrhage by the Intramuscular Injection of Calcium Chloride.—GROVE and VINES (*British Med. Jour.*, July 9, 1921, p. 40) recommend the intramuscular injection of calcium chloride for the treatment and prophylaxis of hemorrhage. The dose employed was 100 minims of a 1 per cent solution, and the injection was deep into the gluteal muscles. A subcutaneous injection is painful and is regularly followed by sloughing. It is not possible to state definitely the action of calcium salts in controlling bleeding. It is probable there is a direct constrictor effect on the bloodvessels, and, furthermore, the increased calcium content of the blood may promote combination between calcium and blood lipoids with a consequent acceleration of clotting. The dose may be repeated at the end of twenty-four hours and again a day later.

Further Report on the Treatment of Sleeping Sickness.—The treatment employed by MARSHALL and VASSALLO (*British Med. Jour.*, May 28, 1921) is a combination of intravenous and intrathecal injections of organic arsenical preparations (neo-kharsican). The theory on which this therapy is based is that the trypanosomes having once reached the cerebrospinal canal were, after a certain time, immune to any medication via the blood stream. It is generally agreed that the intravenous injection of an organic arsenical sterilizes the blood stream in a short time. But a relapse soon occurs, probably because the focus of infections in the central nervous system is not acted upon by the drug in the blood. Hence a permanent cure can be effected only by sterilizing both the blood and lymphatic stream and the cerebrospinal cavity. While it may be early to state positively that the present treatment promotes definite cure, the authors feel optimistic in the face of the results obtained. Several of their cases have gone well beyond a year with one dose of treatment, and they have all invariably improved in health and no trypanosomes have been found in the blood or the spinal fluid, although they have been subjected to repeated and careful investigations.

Renal Irritation in Man from High Protein Diet.—SQUIER and NEWBURGH (*Arch. Int. Med.*, 1921, xxviii, 1) present the clinical histories and laboratory findings of 4 cases of hypertension in which urinary evidence of renal disturbance was slight or absent, before and after short periods of forced high protein-feeding. In each case the appearance of red blood corpuscles in the urine resulted, in 3 cases

albumin was found, having been previously absent; in 1 case the amount of albumin in the urine was markedly increased and in 3 cases a definite increase in eye-ground changes was noted following the meat diet. Neither restricted nor forced protein-feeding had any influence on the blood-pressure in any of these cases. A case of recently active nephritis showed similar results after high protein diet, except that the red blood corpuscles which made their appearance in the urine failed to disappear promptly, as in the first 4 cases, on return to normal diet, but persisted for at least five months. Two cases undergoing this test were found to have kidney impairment which had not previously been suspected. Forced meat-feeding for two successive meals was invariably sufficient to cause the appearance of red blood corpuscles in the urine of 5 normal young men. The authors reach the conclusion that high protein diet in man is a renal irritant.

An Atypical Bacillus Paratyphosus B Infection.—MORGAN (*Bull. Johns Hopkins Hosp.*, 1921, xxxii, 195) reports a case of cystopyelitis following urethral stricture and urethrotomy, and a detailed account of the cultural and biological characteristics of the causative organism is given. The author reviews the literature and points out that, especially during the World War, there have been many reports of similar organisms which fall, in the classification of Bainbridge between B. paratyphosus B and B. enteritides (Gärtner). These organisms have been variously called "B. paratyphosus C," "Inagglutinable B. paratyphosus B," "Paracolon bac.," etc.; but the author agrees with Schultze that they should be considered as a variant of the B. paratyphosus B originally described by Schottmüller (who also first described the clinical picture of pyelitis caused by this organism), when, as in the case described, the organism shows only slight or moderate serological differences from the accepted B. paratyphosus B.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

The Food Requirements of Children. I. Total Caloric Requirements.—HOLT and FALES (*Am. Jour. Dis. Children*, January, 1921) say that in calculating the total caloric requirements of children, there must be considered separately the component parts of which the total is made up. These are the requirements for basal metabolism, for growth, for muscular activity, and the food values lost in the excreta. The basal requirements which have been determined by Benedict and Talbot are highest per kilo at about the ninth month, and steadily fall from this time up to adult life. The food value lost in the excreta normally is a nearly uniform proportion of the intake, about 10 per

cent for all ages after infancy. The requirements for growth are greatest during the period when the growth is most active during the first year of life and during adolescence. They are nearly uniform from the fourth to the tenth or eleventh years. The average for three factors—basal, growth requirements and food values lost in excreta—are nearly uniform for children of the same weight living under the same or similar conditions. The requirement for activity is the only factor which varies widely with different individuals. The great difference in the calculations of different writers, who have estimated theoretical values for total calories per kilo for children, are in part due to the fact that they have not sufficiently considered the different component parts which make up the total. The average caloric requirement of children according to the observations reported in this paper is about 100 calories per kilo at an age of one year or about 9.5 kilos. For boys it falls to about 80 calories at six years or about 20 kilos, and remains practically constant at this value up to the age of fifteen years, the increasing requirements for activity being met by the reduction in the basal requirements per kilo. After an age of about fifteen years or about 50 kilos is reached, the calories per kilo can rapidly be reduced to adult standards of about 48 calories per kilo. The requirements for girls falls to 76 calories per kilo at six years or about 20 kilos, continues at this value until the tenth year, when it rises because the basal requirement is nearly constant while there is an increase in needs for growth and activity. The requirement remains at 80 calories per kilo until growth is complete, and it then falls rapidly to adult standards of about 44 calories per kilo. In these calculations a much higher value for calories per kilo during adolescence has been allowed than that given by others. This seems to be absolutely essential, because of the increased growth needs at this time and the large requirement for muscular activity. According to their allowance the total daily caloric requirement of children of both sexes during adolescence exceeds by nearly 1000 calories the requirements of the adult man or woman of moderate activity. Children who are under weight require more calories per kilo than those who are of average weight for their age. Children who are overweight require fewer calories per kilo than those of average weight.

Calcium in the Blood of Children.—Denis and Talbot (*Am. Jour. Dis. Children*, January, 1921) have modified Lyman's method. They employ citrated plasma (0.1 gm. of solid sodium citrate to 100 cc of blood), and they use a variety of standards for the final nephelometric reading. These standards are made up to contain 0.2, 0.15 and 0.1 mg. respectively of calcium. In 119 samples of blood from patients in the children's ward, irrespective of diagnosis, the maximum figure was 13.5 and the minimum 1 mg. per 100 cc of blood plasma. In 22 normal adults the maximum was 12.1 and the minimum was 7.2 mg. and the average was 10 mg. of calcium per 100 cc of plasma. In 28 cases of rickets, 7 in the acute and 21 in the convalescent stage, some gave calcium values distinctly below the normal, but as some of these were suffering other illnesses such as pneumonia, no definite conclusions could be drawn. In tetany the calcium content of the serum was extremely low. The administration of calcium chloride, 25 grains three times a day, in 2 cases gave a marked increase in the blood cal-

cium in 1 case. Associated with this increase was the disappearance of the symptoms and apparent cure. In cases of convulsions not due to tetany the blood calcium was very low. This was especially true in epilepsy. In 25 cases of lobar pneumonia, bronchopneumonia and acute bronchitis the blood calcium was very low. After the crisis it rose somewhat. There was no calcium excretion during the febrile stage, but there was after the crisis.

The Ulcerated Meatus in the Circumcised Child.—BRENNEMANN (*Am. Jour. Dis. Children*, January, 1921) notes that the ammoniacal diaper occurs less frequently and less severely with cream mixtures than with simple whole milk mixtures or even with dried milk mixtures. This would rule out fat alone as a cause of this condition. The writer thinks that in a milk mixture it occurs less frequently if the fat is relatively higher than the protein and the salts as compared with their normal relative representation in whole milk. It occurs more frequently if the normal proportion is maintained or if the fat is relatively lower than the protein and salts. The condition has been observed in which partly fat free milk was used. The protein and salts must also be considered as possible causative factors. The failure of the ammonia to occur except in connection with the wet diaper in place, together with the peculiar behavior of the ammoniacal diaper would suggest a further non-dietetic factor existing in the diaper itself. The ammonium salts are fairly stable. Alkalies in the diapers have been set forth as the factor responsible for the breaking-up of the ammonium salts. The source of this may be strong alkali soap used in washing and not thoroughly rinsed from the diapers or bedding. Alkaline stools may also set about the same breaking-up of ammonium salts. Bacteria have also been suggested as causative factors. While the whole proposition of etiology is not clear, still it is justifiable to believe that there are at least two factors present: First, there is the excessive excretion of ammonium salts due to lack of balance of the diet, and second either alkaline stool or unrinsed soap in the diaper itself or bacteria, which break up the ammonium salts and liberate free ammonium.

Chronic Tuberculous Hilus Pneumonia in Children.—GREENBERG (*Am. Jour. Dis. Children*, January, 1921) reports 2 cases. He says that extensive tuberculous lesions about the hilus may occur in infants and young children and pursue a rather chronic course. Recovery probably takes place in the majority of the cases even in children under two years of age. The onset in this type of pulmonary tuberculosis is more or less gradual, and there may be no lung signs until after the disease has lasted for some time. Irregular fever, sweating, expiratory obstruction, diminished breathing, with impaired resonance, a positive von Pirquet and a characteristic roentgen-ray picture are among the earlier manifestations. Enlargement of the supraclavicular lymph nodes, positive results from the guinea-pig inoculations of material from lung puncture or of sputum, and the presence of tubercle bacilli in the sputum may be found later in the course of the disease. This form of tuberculosis should be suspected in infants or children with prolonged irregular fever and sweating, with a positive von Pirquet.

Blood Volume in Infants Estimated by the Vital Dye Method.—LUCAS and DEARING (*Am. Jour. Dis. Children*, January, 1921) found great variation in blood volume per cent. in newborn infants, ranging from 10.7 to 19.5 per cent of body weight and from 107 to 195 cc per kilogram, and the pigment volume from 304 to 899 cc. The average for these were blood volume per cent, 14.7; blood volume per kilogram, 147 cc; and pigment volume, 521 cc. Another one of the interesting variations was that found between plasma volume and red cell volume. The plasma volume per cent was small as compared with the relatively high red cell percentage. These findings were fairly constant in the newborn during the first ten days. No reason could be given for the wide variation beyond the fact that the blood during the first few days undergoes a definite adjustment to the new surroundings. From studies on blood protein and blood sugars it is known that a similar wide variation occurs during the first few days before the normal averages are established, and the blood volume undoubtedly goes through this same period of adjustment, when the blood-forming organs are first called upon to function independently of any assistance from the maternal circulation. There does not seem to be any constant relation between blood volume and weight, length or age in hours or days up to the fifteenth day. In the infants from fifteen days to one year of age there was a definite uniformity constant for the individuals, and the variations between individuals were much less marked than in the first fifteen days, the extremes being from 9 to 12.6 per cent, and the average 10.9 per cent. There was a fairly definite attempt to stabilize the blood volume during the first few months; and for any given infant over a period of several months, the blood volume remained at a fairly constant level.

A Study of the Spinal Fluid in Fifty-two Cases of Congenital Syphilis.—KINGERY (*Jour. Am. Med. Assn.*, January 1, 1921), in a study of 52 cases, found an unquestionable diagnosis established by the presence of the accepted symptoms and stigmas of prenatal infection, the presence of definitely positive reports or both. The findings reported were those found in the routine puncture without any reference to any indications or group of presenting symptoms. In every case the patient had remained long enough under observation to substantiate any doubtful findings, and to observe any developing symptoms, or the occurrence of former ones not demonstrable at the time of the first examination. The ages varied from three weeks to twenty-one years of age. Of the total of 52 cases, 15, or 28.8 per cent, presented some deviation from the normal, according to the accepted standards of spinal fluid findings. The cases divided themselves into two groups according to the extent or severity of the infection. The first group I, which only slight changes had taken place up to the time of the puncture, consisted of 4 cases. In 3 of these the Wassermann reaction on the cerebrospinal fluid was 1+; in 2, 2+. In addition the cell count revealed a slight pleocytosis. The highest cell count in this group was 15 and was associated with an increase in solids to like degree. The early central nervous system impairment was clinically substantiated by the presence of chorioretinitis, increased reflexes and in 1 case by severe nerve deafness. The second group comprised the

more severe grades of involvement. There were 11 cases each of which gave a definitely positive Wassermann reaction. There was a striking parallelism between strongly positive Wassermann reactions and definite albumin and globulin increase. There was a striking lack of parallelism between the degree of pleocytosis and the other strongly positive findings. The cell count in these cases varied between 6 and 159. In addition to the interesting changes in the cerebrospinal fluid this group presented clinical symptoms of considerable gravity. Four cases presented the clinical picture of juvenile general paresis. The other 7 of this group presented other involvements of the nervous system. Two of these were distinctly retarded mentally. Four suffered from pupillary and deep tendon reflex changes. The other patient of this group had a severe cutaneous involvement without other demonstrable changes.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

The Effect of Pregnancy upon the Circulation.—At a meeting of the Obstetrical Society of Vienna, in a discussion upon this subject, WENCKEBACH (*Zentralbl. f. Gynäk.*, 1920, Nr. 38) believes that the most important question in a case of pregnancy complicated by disease of the heart or vessels is whether pregnancy should be interrupted or allowed to go to term. One could base such a decision not only on the condition of the heart, but on the question as to whether it is performing its functions. The consideration of such a case includes many factors. One is the question whether the patient has a living child. If she has not, an additional effort should be made to save the life of the infant. The general health, the condition of nutrition, the hygiene of the patient, all the circumstances of her life must be considered. In studying such a case, one must not fail to include the peripheral vascular system, for the condition of this may prove of the greatest importance. Opinions differ greatly as to the prognosis for a pregnant patient having a lesion of the heart. Some are optimistic and others believe it to be of the gravest import. Each case must be judged upon its merits and reliable grounds for judgment cannot be obtained until a concerted study of the subject is made by pathologists, internists and obstetricians. In continuing the discussion, Thaler would interrupt pregnancy in such a patient only when the compensation was failing. A diseased heart with good compensation and with the patient under favorable circumstances furnishes no indication for the interruption of pregnancy. If, during gestation, the heart begins to fail, medical treatment with rest should first be tried. If the patient improves and compensation is established, interference should be postponed. Under such conditions, if one can

control the patient's environment, a pregnancy can frequently be carried on to its normal termination. There is analogy between these cases and those of nephritis complicating pregnancy. In neither case must the condition be considered hopeless so far as the pregnancy is concerned. When, however, we cannot control the failure of compensation by medical means, when complications such as excessive development of nephritis or goitre develop, then pregnancy must be interrupted. The question will then come up as to whether sterilization shall be practised with the ending of the pregnancy. Where there is acute endocarditis, or where the heart lesion developed recently, the indication for sterilization is not so pressing. The worst cases of heart lesion in pregnancy are mitral stenosis. In some cases, however, if the patient can be tided over one pregnancy, a subsequent one may proceed without complications. Under many circumstances the interruption of pregnancy should be accompanied by sterilization. It is interesting to note how rarely death occurs from cardiac failure in pregnant and parturient women. Among 60,000 patients there occurred but 11 such cases. When these cases are analyzed, there were 7 who had suffered from heart lesions for a considerable time before coming to hospital. Three of these patients had serious lesions in the spinal column. In the remaining 4 there was fatal lack of compensation and in 3 of these the patient had grown very rapidly worse just before labor. In 3 cases autopsy showed a recurrent endocarditis. These patients were admitted to the clinic very shortly before death. One patient had been under observation for some time, and without evidence of a serious cardiac condition. This had rapidly developed just before death. The question arises what method of delivery should be practised at term in a patient suffering from a severe heart lesion? Abdominal Cesarean section is undoubtedly best. When one considers the effect of pregnancy upon the general circulation, we find that the influence of the hormone upon the condition of the blood must be taken into consideration. These substances are produced by the epithelium of the trophoblasts. It is thought that their influence upon the circulation in pregnancy is more potent than the mechanical disarrangements occasioned by pregnancy which have hitherto been considered the essential factors. This is seen especially in the vessels of the peripheral circulation and in early pregnancy when the uterus is too small to influence the circulation by pressure. The development of varicosities may also be ascribed to this source and also certain changes in the heart muscle. The hypertrophy of the heart often seen during pregnancy must, to some extent, be the result of the presence of these substances in the blood. We know that the actual quantity of the blood is not increased during pregnancy and hence, if hypertrophy is to develop, it must be from some other reason than the additional labor of propelling a larger quantity of blood. Kautsky considered mitral stenosis the most important condition of the heart in pregnancy. The form seen in these patients is not that observed after the ordinary rheumatic attack, and there is usually accompanying the stenosis mitral insufficiency. Observations show that the mitral orifice is changed in shape and size during pregnancy, and that this does not resemble the congenital condition sometimes seen in newborn children. This condition is observed in women who have had chorea,

sclerosis and ulcer of the stomach. While a moderate degree of stenosis without insufficiency may do little harm, compensation is so apt to fail that one can understand the high rate of mortality. Where stenosis develops after an infection, especially if insufficiency be present, the prognosis is very bad, even though there may be apparently compensation. When such patients come into labor, they are threatened with acute edema of the lungs or rapid dilatation of the heart. In the puerperal period, they are apt to develop endocarditis, sometimes acute and sometimes developing gradually. With regards to aortic insufficiency, we must distinguish three causes: One is rheumatism, another arteriosclerosis and a third syphilis. The last is especially dangerous because the coronary arteries are often involved and during labor the patient may die from sudden dilatation of the heart. Aneurysm of the aorta may develop during labor and this may produce severe complications even in pregnancy by its gradual development. The least dangerous is the rheumatic form, especially if compensation is maintained. There is probably no greater mistake in diagnosis during pregnancy than the frequent recognition of mitral insufficiency. Systolic murmurs are so often heard at the mitral area and also at the pulmonary area with accentuation of the second pulmonary sound that this mistake is not unreasonable. We have often a rapid pulse and some times a capillary pulse in addition. In these cases dropsy is of considerable importance as a symptom. Mitral insufficiency, unaccompanied by involvement of the kidneys and with good compensation is not a very grave condition. In cases where interference must be practised, the choice should be abdominal Cesarean section, under anesthesia by local injection or into the spinal cord in the region of the sacrum. Such anesthesia disturbs as little as possible the intra-abdominal tension and embarrasses the heart to the least degree. The operation should include the resection of the Fallopian tubes for sterilization.

The Treatment of Antepartum Hemorrhage.—At a conjoint meeting of English Medical Societies, TWEEDY (*Proceedings of the Royal Society of Medicine,* November, 1920) stated his well known views concerning the treatment of antepartum hemorrhage. He does not believe that hemorrhage not arising from placenta previa is accidental, and he is strongly impressed with the inaccuracy of those who deal with these cases in estimating the actual amount of blood loss. In the Rotunda Hospital, antepartum hemorrhage is not considered to be present unless it becomes of considerable severity. So many insignificant hemorrhages are not recorded. In 13,924 deliveries, there were 49 cases of accidental and 45 of unavoidable hemorrhage, and in the out-patient service, in 15,543 cases, there were 47 of so-called accidental bleeding. If all hemorrhages are reported, the percentage becomes much greater, and by this method in 3600 deliveries, there were 44 cases of hemorrhage, most of them of little importance. In another hospital 105 cases of accidental hemorrhage were reported in two years, of which 83 subsided when the membranes were ruptured; 7 died and 15 were treated more radically. From this it would be inferred that there were 22 serious hemorrhages. Among Tweedy's 49 patients, there were 22 in a serious condition treated by packing the vagina; 2 hospital patients died and 7 in the out-

patient service. In 5 of the 7 the tampon was used. He thinks that the 2 deaths in hospital arose from intraperitoneal hemorrhage. In 1 not more than a pint and a half of blood was in the uterus and in the other, the patient was delivered by natural labor, dying after the third stage. In Tweedy's later work at the Rotunda, in three years he encountered 23 cases of accidental hemorrhage. Acting upon the knowledge that this complication often arises from toxemia complicating pregnancy, Cesarean section was performed when toxemia was producing the hemorrhage. Three of these operations were done successfully, and in all 3 there was blood in the abdominal cavity and in 1 the ovarian artery beneath the Fallopian tube was bleeding. Of the remaining 21 cases, 8 were treated by the tampon. There were no deaths from loss of blood, but 1 woman died from sepsis ten days after delivery. Taking both series of cases together, there were 72 in 18,000 deliveries with 2 deaths. In 30 the tampon was used. Before this method was adopted in the institution, in 3600 patients, there were 5 deaths. The writer is convinced that the use of the tampon is valuable because it impedes the circulation in the uterine vessels. It also causes the uterus to contract. The writer believes that the efficiency of the treatment depends on the way in which it is applied. The left hand should be passed into the vagina, with the palmar surface directed toward the hollow of the sacrum and the tips of the fingers lying behind the cervix. Small pieces of cotton wool, squeezed out of lysol solution, each the size of the thumb knuckle, are then taken and inserted by means of the right hand around the cervix. The fingers of the left hand are utilized to squeeze the pellets into a compact mass, forcing the spaces between them to permit the insertion of other pellets. This process is continued from above downward until the vulva is reached and no more cotton can be inserted. A T-bandage is then applied to keep the tampons in position and an abdominal binder is fastened tightly from above downward, and when it is removed, only so much blood will be found as escaped during the operation. Its application is not easy, nor without danger. If the first effort to stop bleeding in this way is not successful, the tampon must be removed entirely and the attempt repeated. Pain, distress and some shock follow its application and the mucous membrane of the vagina is wounded, rupture of the uterus may occur. The writer believes that in the vicinity of the internal os intraperitoneal hemorrhage is controlled by this method. A leak from an ovarian artery would not be prevented. The writer believes that hysterectomy is not indicated in accidental hemorrhage. He also states that the fact that the membranes have ruptured does not contraindicate the treatment.

In discussion, Shaw, of Manchester, had not used the method of packing because he believed that it predisposed to septic infection, and that, as applied by the general practitioner in private practice, it is not only dangerous but inefficient. His method consisted of rupturing the membranes, applying an abdominal binder tightly, and giving ergot or pituitrin. Williamson, at St. Bartholomew's Hospital, in 2600 patients had 98 cases of antepartum hemorrhage, with a mortality which varied in the different groups of cases. They were treated by various methods, and his experience had convinced him that tamponing the vagina is a valuable method in the treatment of antepartum hemorrhage and by

this bleeding in many cases can be arrested. He believes that cases of concealed hemorrhage caused by toxemia require Cesarean section, if uterine contractions are absent and the cervix is not dilated. In cases which are not toxemic, he would employ the tampon until dilatation developed, when he would practice bipolar version or introduce de Ribes' bag. He believes that the tampon acts by stimulating muscular contraction and he does not believe that it can check hemorrhage by pressing the uterine arteries.

In discussion, the majority of opinions seemed to be that midwives should not be shown how to apply a vaginal tampon; that if the method is taught to students, it should be taught as thoroughly as possible and that great stress should be laid upon the necessity for careful antisepsis.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Fibroids of the Ovary.—Ovarian fibromata comprise approximately 2 per cent of all ovarian tumors and may occur from the time of puberty to an advanced age. The majority occur in single women about the time of menopause. The size and weight of these tumors vary extremely and the etiology has always been obscure. In reporting a case of this rare disease, CLARK and GABE (*Am. Jour. Obst. and Gynec.*, 1921, i, 603) state that in the majority of the reported cases patients have complained of a swelling of the abdomen, pain of varying degree, often none at all, and not infrequently of feeling a hard mass through the abdominal walls. Other symptoms, such as frequency of urination, constipation, etc., are due to varying mechanical factors. Objectively, the tumor is usually palpated without difficulty. Its consistency, mobility and unilateral occurrence are significant. One feature, however, is of marked diagnostic importance when present, namely, ascites. The weight attached to this finding has been especially emphasized by English writers on the subject. It may be recalled that fibroma elsewhere, and especially in the uterus, is rarely associated with ascites. The presence of ascites with intra-abdominal carcinomatosis, located either primarily or secondarily in the ovary as a tumor mass, is common, but is associated with many other signs and symptoms not found in fibroma of the ovary. In other benign tumors of the ovary, ascites is usually lacking. It, therefore, seems of considerable diagnostic importance to find ascites together with a unilateral adnexal tumor in a case lacking signs of cachexia, great loss of weight, or symptoms

pointing to a focus of malignancy elsewhere in the body, as in the breast or stomach. In the absence of ascites, differential diagnosis from that of other adnexal tumors offers considerable difficulty. The tendency of ovarian fibromata to be unilateral, movable and hard, should be borne in mind. In the presence of ascites, where nephritis, cardiac decompensation, portal obstruction, abdominal carcinoma, tuberculous peritonitis, and the anemias can be ruled out, the occurrence of such findings should make one very suspicious of ovarian fibroma. The treatment, without exception is operation. The prognosis, as indicated from case reports, is excellent. The pathology of ovarian fibroma has been carefully studied by several investigators, showing that these tumors vary in size. Their consistency, likewise, is extremely variable, some, composed of a loosely woven network of connective tissue, being soft, while others require the use of a bone saw for their section. In a similar way, their shape, appearance on cross-section, color and general outline cover a wide range of possibilities. They show many forms of degeneration and it is on account of these as well as the possibility of a twisted pedicle, that their removal should be urged. The court of final judgment is the microscopic appearance of the tumor.

Treatment of Border-line Cancer of the Cervix.—In the opinion of WEISS (*Am. Jour. Obst. and Gynec.*, 1921, i, 661), cancer of the cervix is still to be classed as an operative condition when discovered early and the patient is a good risk. When a doubtful border-line condition is presented, treatment by radium is advisable and the question of subsequent operation should be determined by the reaction obtained; but if operation is contraindicated by age, general condition, heart, kidney or bloodvessel, radium alone should be used. A careful comparison between the cautery and radium type of treatment shows that both have advantages and disadvantages and that, in carefully selected border-line cases, far better results are obtained by a judicious combination of cautery amputation followed by moderate doses of radium. The author's results in a small series of border-line cases, while generally satisfactory, are far from conclusive. Similarly, the wide range of radium dosage in treating cervical cancer, varying from 1500 mg. hours in some clinics to 8000 mg. hours in others shows that no definite conclusions have been reached, and while favorable reports have been received from both extremes, the use of radium is still somewhat empirical. Definite conclusions can be drawn only after a definite tabulation of a long series of cases based on follow-up and end-results.

Clinical Experience with Corpus Luteum Extract.—The distressing symptoms of the menopause may be relieved quite frequently by the administration of corpus luteum extract, according to LEIGHTON (*Am. Jour. Obst. and Gynec.*, 1921, i, 613), since luteum extract supplies that element so necessary to the woman during her normal menstrual life. This therapy exerts its greatest benefit in the treatment of those women who have begun to exhibit the early manifestations of the climacteric. To avoid the unsatisfactory results which have been reported by some gynecologists, it is necessary that luteum extract be administered early and continuously once the diagnosis is made. Procrastination on the part of either the patient or the physician often means ill success, When menstrual irregularity makes itself known and the hot flushes.

mental confusion, tremor and hyperthyroideal symptoms are first evident, then is the proper time for ovarian organotherapy, not waiting until the height of the disorder has been reached or the woman has suffered for months or years with a "chronic" menopause. Early control is necessary and, once obtained, it is of easy maintainence. In over half of the 300 or more women to whom Leighton has given luteum extract, the indication for its use was solely the menopausal syndrome. Of this number there were not over a dozen who could not report exceptional benefit, even to absolute relief. To those women who during the menstrual life complain of so-called "sick headaches" of the frontal and temporal type, with nausea and vomiting, which occur with peculiar periodicity, at or about the time of menstruation, ovarian organotherapy offers much relief. In chlorosis, as an adjunct to hematinics, luteum is also indicated. The functional amenorrhea of women, in early adolescence or mid-menstrual life, responds in a miraculous manner. In the use of thyroid as a "reduction cure" the giving of luteum at the same time seems to obviate the occurrence of profuse sweating spells, muscular weakness, tachycardia, nausea and other vasomotor symptoms, occasionally following the ingestion of thyroid extract. Larger doses of thyroid are tolerated, if given in combination with luteum. While Leighton has not had 100 per cent of success, it has been his fortunate experience to observe a relief and cessation of many disorders, referable to deficient ovarian secretion, where proper diagnosis is followed by the continuous, thorough and regular use of luteum extract. It is important above all, that one should prescribe and the patient obtain a product from recent fresh material and care must be taken to see to it that the dispensing chemist has such on hand. The indiscriminate buying of luteum extract is one thing which Leighton is careful to prevent. A patient is directed to the shop where he knows fresh tablets are to be had. Each prescription calling for such, bears on the direction label, "These must be taken for ten of twelve weeks," and special emphasis is laid upon this point. He explains every time, at the commencement of treatment, that it is cumulative in action, that it is non-toxic, when fresh, and that one must be conscientious in its taking, as results are obtained slowly and relief is not immediate.

OPHTHALMOLOGY

UNDER THE CHARGE OF

EDWARD JACKSON, A.M., M.D.,

DENVER, COLORADO,

AND

T. B. SCHNEIDEMAN, A.M., M.D.,

PHILADELPHIA.

Treatment of Hysterical Amaurosis, Hemeralopia and Amblyopia by Suggestion and Hypnotism.—AUGSTEIN (*Ztschr. f. Augenheilk.*, 1920, xxiii, 47) calls the attention of ophthalmologists to the importance of

psychotherapy. In contrast to a preceding period, practitioners have laid too little stress, during the last ten years, upon the marked therapeutic effects of this method in the treatment of disease; indeed by many it has been regarded as unworthy of the scientific physician. The writer, based upon an extensive material, seeks to demonstrate the value of various psychotherapeutic methods; he has succeeded in curing by such methods hysterical hemeralopia and amblyopia. He cites a remarkable case of binocular amaurosis, the only symptom of hysteria demonstrable, which was cured by hypnotism after continuous blindness of twenty-one months. Such amaurosis is, in the author's opinion, solely the consequence of traumatism; the cause is to be sought in an injury of the highest centers of the cerebral cortex, determined in all probability by autosuggestion. The same influence also explains hysterical stasis of the pupil as well as the sluggish reaction sometimes observed in hysteria. Some trauma of material or psychic nature may well be regarded as the sole cause of hysteria, or as the determining factor where a predisposition to that neurosis exists. Every form of hysteria is a disturbance of normal brain function. As regards treatment, suggestion in connection with the faradic and galvanocurrent and injections of sodium chloride as a placebo, are as a rule, adequate for the cure of hysterical disturbances of the vision; the slight pain experienced from these agents plays a certain role in the cure; but in many cases hypnotism is indispensable; when properly conducted the application is never injurious.

Strychnine in Ophthalmology.—Leoz (*Arch. d. Oftal.*, 1921, i, 6) remarks that strychnine is a therapeutic agent which oculists sometimes employ, without much confidence, in desperate cases, but which, he thinks, can give good results if persevered in and in fairly large doses by injection. The medicament is evidently useless in complete optic atrophy and in peripheral paralyses of ocular nerves from compression or section; it is contraindicated in mydriasis dependent upon irritation or functional exaltation of the sympathetic. It finds its indication in pareses and paralyses of dyscrasic, toxic or infectious origin, in those dependent upon small nuclear hemorrhages and even in some cases of tabes; in non-paralytic latent strabismus, in muscular and accommodative asthenopia and especially in all such manifestations occasioned by general fatigue and exhaustion. Its value is undeniable in the so-called toxic amblyopias; it should likewise be employed in atrophic neuritis, retinitis and choroiditis, and in those grave cases in which nothing is to be hoped from any other treatment. To obtain definite results the initial dose should be 1 or 2 mg., to be increased to the point of tolerance and continued for some time, and repeated after intermission. By this method the author has been enabled to reach 76 mg. and even 82 mg. at a single dose. He begins with 1 or 2 mg., according to the patient's weight, for five days consecutively, then doubles the dose for five more; abstention for six days, followed by six injections of 3 mg., again followed by six days of withdrawal, when further injections of 4 mg. are given and so on up to 15 or 20 mg. The treatment is then to be suspended for two months and then resumed with larger doses to the point of tolerance. The symptoms of intolerance are well known: the most important are muscular jerking of the

extremities; a general sensorial excitability is frequently present; pruritus, tingling and great sensitiveness to sounds and jars. The writer has never met with any serious accidents.

Ocular Disturbances Consecutive to Inflammation of the Middle Ear.—GERDIL (*Paris Thèsis*, 1921) observes that ocular complications in the course of otitis media consist of paralysis of the abducens, encountered in 9 per cent of such cases, and papillary stasis with or without neuritis; the latter is of extremely frequent occurrence, being noted in 60 per cent of recorded observations. Paralysis of the sixth motor nerve is met with particularly in the course of the intracranial complications of otitis; it is due to quite diverse causes, such as circumscribed meningitis, cerebellar abscess, and thrombophlebitis; cases have, however, occurred in which the paralysis was not accompanied by intracranial complications; the pathogeny of such cases is very difficult of explanation; very probably the underlying condition is an affection directly involving the nerve. The alterations of the optic nerve in the course of otitis are of two forms: simple papillary stasis without immediate functional signs with ventricular hypertension alone; stasis with neuritis and rapid failure of vision when ventricular hypertension supervenes upon meningeal infection along the sheaths of the optic nerve. Systematic examination of the fundus, in the course of otitis media accompanied by symptoms of wider involvement, will reveal these alterations of the optic nerve. Treatment is based upon early diagnosis; good results may be obtained, particularly in papillary stasis. Lumbar puncture is of value in cases of slight hypertension, but it must be repeated several times. In cases of hypertension with papillary stasis recourse should be had to a decompressive craniotomy; to be of use, intervention should be practised before atrophy has had time to occur. In stasis with neuritis, vaccinotherapy is indicated, especially where the infectious organism has been isolated.

Amaurosis Provoked by Lightning.—Amaurosis from lightning is rare. An exhaustive study by VAN LINT, presented to the Belgian Society of Ophthalmology, November, 1909 embraced but 3 cases since 1843. DEPAS (*Clin. opht.*, 1921, xxv, 63) reports the following case: A young woman being in her kitchen during a violent thunderstorm, with the window open, experienced the impression that lightning was passing through the room, when she suddenly became blind; she collapsed without, however, losing consciousness, and was found in this condition shortly after. There were no appreciable lesions except two superficial red spots on the upper part of the breast and arm; they resembled urticaria, and disappeared in a short time. She was seen by the reporter two hours after the accident; there was such intense photophobia that examination was difficult. Blepharospasm was so severe as to be uninfluenced by cocain; ophthalmoscopic examination was impossible. The examiner could only discover slight hyperemia of the conjunctiva, and that the pupils, somewhat contracted, reacted normally. Vision was almost nil; there was a red cloud before the eyes, through which the test-card could be distinguished as an obscure whitish surface. Nevertheless the presence of the luminous reflex justified a favorable prognosis. Two days later there was not only no improvement but the sight was

even worse; pupillary reaction was still normal. An interesting fact to note is that during these two days very intense ocular and periorbital pain, with cephalalgia so severe as to prevent sleep, had appeared; three days later amelioration began; ophthalmoscopic examination failed to show the slightest trace of any lesion. From thence onward improvement was rapid, with perfect restoration of sight three weeks later, with normal fields. A first explanation of the loss of vision would ascribe the same to hysteria; but in view of our entire ignorance of the intimate mechanism of the act of vision it is possible that that mechanism may have been paralyzed for a period without alteration of the conductibility of the nervous fibers. Another conclusion from this case is that, independent of its visual properties, the retina also possesses sensation, otherwise it would be impossible to explain the intense pain provoked by light while vision was absent, and there was no external lesion capable of explaining the intense photophobia present. To this same sensory property may also be attributed the hyperesthesia to light which becomes a truly painful sensation in many persons exposed to intense light without the presence of any objective lesion.

Therapeutic Value of Injections of Milk in Diseases of the Eye.—CASSIMATIS (*La clin. ophthal.*, July, 1921, p. 378) gives his conclusions upon the value of this method of treatment based upon 604 injections in 134 patients, of whom, however, only 84 could be followed up regularly. The author's technic consisted in making the injections most usually deeply into the gluteal muscles, rarely into the subcutaneous tissue; he has never employed subconjunctival injections. The method is entirely harmless as regards both the eye and the general system. The treatment is para-specific, constituting a powerful therapeutic method as an adjuvant to appropriate local measures; the latter should be applied in every case. The injections should not be regarded as a panacea for all ocular affections; they are capable of real service as an adjuvant in all infections of the cornea and uveal tract, more especially in ulcer with hypopyon, rheumatic iritis and purulent conjunctivitis. They are also indicated in all operations in which postoperative infection is to be feared. They should be practised as early as possible, and in sufficiently large doses, although favorable effects upon the inflammatory process occur even in the later stages.

Atropin in Ophthalmology.—FRENKEL (*Arch. d. ophthal.*, July, 1921, p. 385) observes, from the fact of its great utility in ophthalmology, that there has been a tendency to overuse or abuse of this powerful drug; in fact, there has been a regular periodicity of protests which have been well summarized by Serie in his inaugural thésis. As an instance of the excessive use of atropin, the writer mentions all forms of keratitis, especially the superficial; this has been so distinctly recognized that certain writers have even recommended eserin in its place. He lays down as the principal indication for the use of atropin, iritis and associated conditions, such as cyclitis, iridocyclitis and interstitial keratitis, an affection so frequently complicated with cyclitis. Whether the iritis be primary or secondary, atropin is the remedy unless the inflammation depends upon some systemic condition which may also occasion hypertension; this is the case with certain forms of iritis in diabetes,

of iritis with a tendency to hemorrhage in ocular arteriosclerosis and also in certain cases of cyclitis occurring in the course of interstitial keratitis. Iridocyclitis from unrecognized intra-ocular foreign bodies (Morax) may also be accompanied by hypertension. Finally, atropin is also indicated in iritis complicating hypopyon and other exogenous infections. On the other hand the remedy is not indicated in non-suppurative superficial keratitis, scrofulous, lymphatic, impetiginous forms of keratitis, pannus or herpetic keratitis not accompanied by iritis. In these affections it is not only useless but even injurious by increasing the photophobia. Eserin, or better still, pilocarpin, is preferable in these forms of superficial keratitis. Atropin appears also to be contraindicated in keratitis from vesicating gases or superficial burns without secondary infection, as also in electric keratitis. In bullous and filamentous keratitis, and in superficial erosions of the cornea, pilocarpin is superior to atropin. In episcleritis and scleritis the employment of atropin should depend upon the presence or absence of cyclitis or iridocyclitis as well as the state of the ocular tension. This is the guide also to its use in affections of the posterior segment such as non-neoplastic detachment of the retina. Although the treatment of strabismus by atropin has now fallen into disuse the method is of some value as an adjuvant to orthoptic treatment. True intolerance is due rather to improper indication or a septic condition of the solution used rather than to idiosyncrasy as invoked by the older writers. Among the succedanea of atropin, scopolamin is more toxic and should be used with discretion. The usual concentrated solution of atropin, 1:100 is too strong, even for exceptional cases; 1:200 is always sufficient if the proper treatment of the exciting disease (usually specific) is also given. Adrenalin adds to the efficiency of weaker solutions. As a résumé of the indications for atropin, Frenkel would subordinate them all to exact diagnosis of the ocular and systemic conditions and to the state of the intra-ocular tension.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Studies on the Relation of Mineral Dusts to Tuberculosis: (1) The Relatively Early Lesions in Experimental Pneumokoniosis Produced by Granite Inhalation, and their Influence on Pulmonary Tuberculosis—GARDNER (*Am. Rev. Tuberc.*, 1920, iv, 734) exposed large numbers of guinea-pigs to granite dust over varying lengths of time by means of a special apparatus. The guinea-pigs were infected with a strain (R′)

of tubercle bacilli, preceding, during and following the dust exposure by spraying with a de Vilbiss vaporizer. Control animals received either dust alone or tubercle bacilli alone. The lungs were prepared for microscopic examination after the methods of Miller, where intratracheal instillation of the fixative followed by removal *en masse* was employed. When only dust was given, small quantities of it could be found after three weeks' exposure, but it could not be recognized macroscopically until the seventh month. The dust was first encompassed in mononuclear intra-alveolar cells, the origin of which, the author believed, was reduced to a consideration of the local vascular endothelium, or the transitional cell of the blood-stream. In two months, the intra-alveolar dust cells mobilized, lying in the alveoli along the ductuli alveolares, and about the proximal sides of the alveoli adjacent to vessels and bronchioles. During a period of from three to seven months the process steadily increased, the invasion of lymphoid tissue becoming more extensive, and the larger nodules at the bifurcation of the bronchi becoming involved. If the dusting process were stopped, the lung rapidly attempted to remove the irritant, which was not found in mononuclear cells near enlarged lymph nodes, some, however, remaining within the aveoli along the ductuli alveolares. The first mobilization of the dust was within the air spaces, through which it was carried to the nearest lymphoid tissue, where it gained access to the lymphatic system and was removed from the lung. When inhalation of only tubercle bacilli was instituted by the twenty-nine-year-old strain (Ri), large, proliferative, subpleural tubercles with caseous centers appeared in three weeks. After two months these tubercles shrank and the midzonal tubercles increased in size. At six or seven months many of the lesions had practically disappeared, having healed with a morphological and functional restoration. In the coincident dust and infection experiments, the tubercles were more numerous, larger and had less tendency to a regular zonal arrangement. While the degree of caseation was not affected, an early and progressive fibrosis resulting from the stimulation of the dust not only distorted the tubercle, but retarded its healing. It would appear from these researches that both irritants—the dust and the bacilli—"enter and leave the lung by the same path." From his work to date, the author concluded that tubercles occur more frequently and tend to run a more prolonged course in the dusted than the undusted lung, and that the advent of the tuberculous process to the regional lymph nodes is not prevented.

Leukoplakia of the Pelvis of Kidney and Ureter.—RICHEY (*Jour. Lab. and Clin. Med.*, 1920, v, 635) reported a case of leukoplakia of the pelvis of right kidney and ureter from a man, aged forty-three years, who for twenty-two years had experienced periodic paroxysms of pain following an injury to the back. The kidney showed an advanced suppurative pyonephrosis, the leukoplakia, occurring as a white silvery, finely wrinkled membrane, looking not unlike the delicately corrugated skin of the scrotum of infants. Microscopically, the lining of the pelvis and ureter consisted of a thick layer of stratified squamous epithelium, presenting a large amount of keratinization of the free surface. No membrana propria could be demonstrated, the deepest layer of epithe-

lium resting directly upon a bed of granulation tissue. The culture of the urine yielded B. coli communior and B. acidi lactici. The author explains leukoplakia of the renal pelvis and ureter upon the theory of metaplasia "as a histogenic transformation induced by the alteration of environment, wrought by a long standing inflammatory process, with a resultant change in morphology of the cells from the normal transitional to stratified squamous epithelium even to the formation of a superficial layer of keratin."

The Sachs-Georgi Precipitation Test for Syphilis.—For several years investigators have attempted to find a test for syphilis less elaborate and complicated than the Wassermann test, and if possible, more delicate and specific. These endeavors have usually been directed along lines of precipitation tests. Some of them have been partly successful, but with the exception of the Lange colloidal-gold test on spinal fluid, none have been generally adopted. HULL and FAUGHT (*Jour. Immunol.*, 1920, v, 521) described a modification of the Sachs-Georgi test, using clear blood serum (0.3 cc) and an alcoholic extract of beef heart (1 cc), either cholesterinized or not. The entire volume of the test is 1.3 cc instead of 10.5 cc as advised in the original procedure. The authors emphasized the importance of vigorous shaking of the antigen when diluting it (1 to 5) with normal salt solution and of titrating the antigen to determine the optimum amount of precipitation. The prime requisite for the serum was its clearness, age and inactivation apparently making no difference. Centrifugalization enabled an immediate reading. As a rule, positive tests can be read when allowed to stand overnight. No change was noted after forty-eight hours. Optimum results were obtained with low temperatures for incubation, though no appreciable difference was noted in overnight incubation at room temperature and at ice-box temperature. Parallel precipitation and Wassermann tests were observed in 296 instances. Eighty-eight per cent of the samples agreed; in 7 per cent, the precipitation test showed a more delicate reaction, being positive where the Wassermann was negative; 2 per cent yielded a negative precipitation test with a definitely positive Wassermann, and in 3 per cent it was negative when the Wassermann was doubtful. Treatment of the patient apparently affected the results of the precipitation, causing it at times to become negative while the Wassermann was positive. Attempts to determine whether the precipitate formed in the Sachs-Georgi test was entirely responsible for the Wassermann reaction were unsuccessful. Similarly, TANIGUCHI (*British Jour. Exper. Path.*, 1921, ii, 41) compared the results between the Wassermann and Sachs-Georgi reactions on 296 cases. Ninety-one per cent gave the same result, while discrepancies were encountered in the remainder. The authors did not regard any of the discrepancies as serious, noting that the largest proportion occurred in cases which were suspicious to the Wassermann test but negative to the Sachs-Georgi reaction. When compared with the findings of other investigators, they felt that the discrepancies were, in all probability, not due to any essential difference in the nature of the two reactions and that, in general, the differences have been observed only in case of weak or doubtful reactions. The technic was essentially that as modified by Sachs-Georgi

and known as the "incubator method," where the readings were made after keeping the mixture for eighteen to twenty hours at 37° C. The alcoholic human heart extract, as used in the Wassermann reaction, was prepared by the double method. The human sera were inactivated by heating thirty minutes at 56° C. To each of two tubes containing 0.5 cc of emulsion a volume of 1 cc, consisting respectively of 0.1 and 0.05 cc serum diluted with saline, was added and mixed by slight shaking. From a practical standpoint, the authors believe that the Sachs-Georgi reaction suffers from the greater difficulty of distinguishing between negative and suspicious or weakly positive reactions. It was found that the precipitable substance in the Sachs-Georgi reaction consisted mainly of the lipoids contained in the emulsion. In a *resume* of the results of 1042 examinations, on serums and cerebrospinal fluids made with the Wassermann and Sachs-Georgi tests, LEVINSON and PETERSEN (*Arch. Dermat. and Syph.*, 1921, iii, 286) found a close parallelism of the two reactions (92 per cent). In 62 cases in which the Wassermann reaction was negative while the Sachs-Georgi reaction was positive or doubtful, the clinical history or examination revealed evidence of syphilis in 58 per cent. The authors employed a technic as modified by Mandelbaum, differing from the original in the use of smaller amounts of serum and antigen. Emphasis was placed on the preparation of a proper antigen and the careful reading of results. No superiority of ice-box over simple room temperature incubation was found. Because of its simplicity and the fact that it is frequently positive in syphilitic cases when the Wassermann test is negative, the authors are of the opinion the Sachs-Georgi reaction offers a valuable aid in the routine examination of syphilis when used in conjunction with the Wassermann reaction. KILDUFFE (*Arch. Dermat. and Syph.*, 1921, iii, 416) reported the results of parallel Wassermann and Sachs-Georgi tests on 296 human sera. The technic for the latter test corresponded to that described by Galli-Valerio. Twenty-three per cent gave positive Wassermann reactions while in the Sachs-Georgi tests the total number of positive reactions was 14 per cent, some of which were in Wassermann negative sera. By the Wassermann, 70 per cent were negative while by the Sachs-Georgi, 60 per cent were negative, some of these occurring in Wassermann positive sera. Of 16 anticomplementary serums, 2 gave a weakly positive Sachs-Georgi reaction. Twenty-three sera reacted only with the cholesterinized heart extract and the acetone insoluble lipoid extract, the syphilitic liver extract being negative; of these 6 gave positive Sachs-Georgi reactions. The worker concluded that a diagnosis of syphilis or a conclusion as to treatment cannot be based on the results of a Sachs-Georgi test with safety.

Tuberculosis in Guinea-pigs with Experimentally Produced Endothelial Leukocytosis.—MCJUNKIN (*Jour. Med. Research*, 1921, xlii, 2–201) studied the effect on tuberculous guinea-pigs of producing in them an endothelial leukocytosis by the intraperitoneal injection of cultures of B. phlei, B. smegmatis, and non-virulent tubercle bacilli. The type of leukocyte increased was the large mononuclear of transitional leukocyte which was differentiated by the benzidine polychrome stain. It was found that those tuberculous animals in which the leu-

kocytosis had been induced usually lived a few days longer than the control untreated tuberculous guinea-pigs. The chief difference in pathological features at autopsy was that the spleen of the treated animals was quite small, bound down by adhesions, and was free from definite tubercles, while in the untreated tuberculous animals the spleen was enlarged and showed necrotic areas.

HYGIENE AND PUBLIC HEALTH

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MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Experiments on Alastrim.—LEAKE and FORCE (*Public Health Rep.*, 1921, xxxvi, 1437), working with material in the shape of crusts and vesicle contents from cases of alastrim, a mild form of smallpox or a smallpox-like disease, found that the virus immunized monkeys against vaccine virus. Rabbits gave similar results, while rabbits previously inoculated with vaccine virus showed cutaneous sensitization to smallpox, alastrim and vaccine virus, but were negative to chickenpox. The authors hold that this work indicates the identity of alastrim and smallpox.

A Guide to the Proper Rat-proofing of Buildings.—HAUER (*Public Health Reports*, 1921, xxxvi, 930) points out that trapping and poisoning result in only temporary reduction of the number of rodents in a community, though these measures are valuable in a plague emergency. On the other hand, rat-proofing gives lasting results, though the warning is given that we cannot expect to make any community rodent-free. The classification of buildings according to rat hazard and subclassification with reference to construction and uses are given, as are the measures applicable to each group. Details of the proper use of concrete and of other important features of rat-proofing are given.

Industrial Dermatosis Among Printers.—MCCONNELL (*Public Health Reports*, 1921, xxxvi, 979) investigated an eruptive condition known as "ink poisoning" among printers. The condition was found only among those who have "dry" skins and was not accompanied by any constitutional symptoms. The lesions varied from erythema to ulcers and were confined to the regions exposed to the ink. A calamine gelatine paint was found to remedy the dermatitis promptly. As a prophylactic it is recommended that lanolin or a mixture of lanolin and olive oil be rubbed into the hands and forearms.

Anopheles and Sea-water.—GRIFFITS (*Public Health Reports*, 1921, xxxvi, 990) reviews earlier observations on the subject and records his own experiences. The latter lead to the following conclusions: (1) *A. crucians* was found to propagate in sea-water diluted to a maximum salinity of 10,088, or slightly more than 50 per cent average sea-water. The transfer to sea-water of *A. crucians* larvæ which had started their development in brackish water did not unfavorably affect their subsequent development. (2) *A. quadrimaculatus* was not found to breed in numbers sufficient to be of sanitary importance in a higher salinity than 10,003, or 1.5 per cent sea-water. In one case two larvæ found in water with a salinity of 10.048 developed into *A. quadrimaculatus* imagoes; but this observation requires confirmation as to whether this species may complete its entire water cycle in so high a percentage of sea-water. The question is raised as to whether *A. quadrimaculatus* larvæ may not withstand a much higher salinity intermittently than continuously. Specimens of *A. quadrimaculatus* transferred from fresh pond-water to sea-water, salinity 10,160, were all killed within twelve hours. (3) *A. punctipennis* was not found developing in salt or brackish waters. This species breeds under a wider range of conditions than either *A. quadrimaculatus* or *A. crucians*, but apparently does not survive in salt or brackish waters. Larvæ of *A. punctipennis* all died within seven hours when put into sea-water.

Typhoid Fever in Cleveland, Ohio, for the Years 1918, 1919 and 1920.—PERKINS (*Public Health Reports*, 1921, xxxvi, 1095) gives a detailed discussion of recent experiences in Cleveland with typhoid fever, considering especially the possible sources of infections. The evidence excludes flies and milk as sources of any appreciable amount of infection; food, contact, and infection acquired by bathing in contaminated water are allocated a fairly definitely though relatively small number of cases. The city water supply, though part is filtered and all is chlorinated, is regarded as the chief source of infection. The author does not regard the chlorination as adequate to make the water supply safe, a point on which the water department of the city disagrees. A plea is made for the providing of a supply which shall at all times conform to Federal requirements from a bacteriological point of view, *i. e.*, not to exceed one colon bacillus in 50 cc. It is noted that whenever an improvement has been made in Cleveland's water supply a drop in typhoid incidence has followed.

Recovery from Rabies, with Reports of Cases of Treatment Paralysis and of Recovery of Animals Apparently Rabid.—PHILLIPS, BERRY and SNOCK (*Jour. Infect. Dis.*, 1921, xxix, 97) state that spontaneous recovery from rabies naturally acquired, while rare, does occur. The saliva of an animal which recovers from rabies may have been extremely virulent during the course of the disease. As early as thirty-eight days after recovery from street rabies in a dog, the infectivity of the brain may disappear and Negri bodies be absent. And that therapeutic measures to control the symptoms in developed rabies in man should not be so heroic as to themselves endanger the life of the patient, for there is a possibility of recovery.

Fake Arsphenamine.—(*Public Health Reports*, 1921, xxxvi, 1510). The Public Health Service issues a warning in regard to spurious arsphenamine, quoted from the weekly Bulletin of the Health Department of the City of New York: "The Department of Health having made an investigation relative to the sale, in the city, of arsphenamine of supposedly German origin, by seamen and other unscrupulous venders, submitted several samples purchased to its chemical laboratory for analysis. The chemist's report shows the samples to be a fraudulent substitution, being a combination of sodium chloride and a yellow dye. Physicians and druggists are accordingly warned against purchasing such products from unknown persons."

Observations on the Spread and Persistence of the Hemolytic Streptococci Peculiar to Scarlet Fever. The Streptococci Isolated from Attendants and Surroundings of Scarlet Fever Patients.—TUNNICLIFF, (*Jour. Infect. Dis.*, 1921, xxix, 91) states that hemolytic streptococci may be isolated from the floor and walls of rooms occupied by patients with scarlet fever and diphtheria, and from the fingernails, face masks and shoes of the attending nurses and from the eating utensils used by patients harboring hemolytic streptococci. Only 5 of 20 strains thus isolated were opsonified and agglutinated by the serum of a sheep immunized with a hemolytic streptococcus from scarlet fever and hence to be considered as specific for scarlet fever. Four of these strains were isolated from the eating utensils of scarlet fever patients and one from the face mask of the nurse in attendance. These results indicate the value of face masks and the necessity of disinfection of eating utensils used by patients with infectious diseases. It would appear also that persons associated with scarlet fever patients may develop tonsillitis without an exanthem and harbor hemolytic streptococci which belong to the same biologic group as those isolated from typical cases of scarlet fever. Agglutination of hemolytic streptococci from suspected cases of scarlet fever, by immune sheep serum specific for streptococci from scarlet fever, has proved helpful in diagnosis. These results suggest, further, that while patients with scarlet fever generally rid themselves of hemolytic streptococci specific for scarlet fever in from three to four weeks, patients with discharges may retain them much longer, and that the streptococcus specific for scarlet fever disappears at the time when the patient becomes non-infectious, according to clinical experience.

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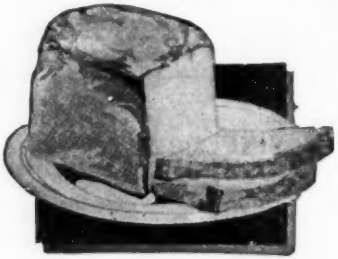

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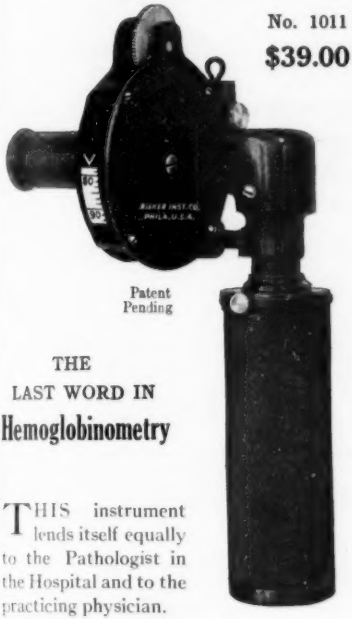

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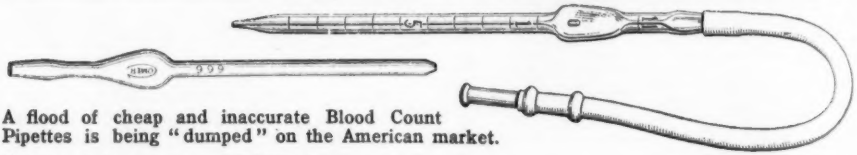

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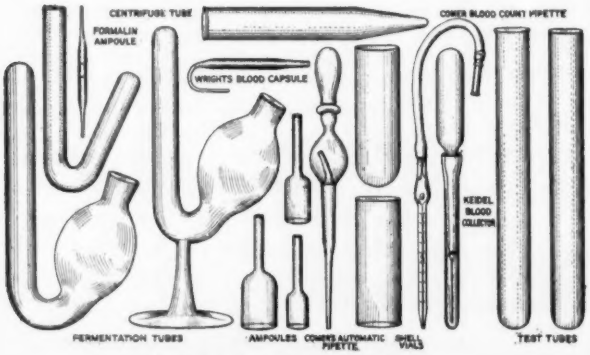

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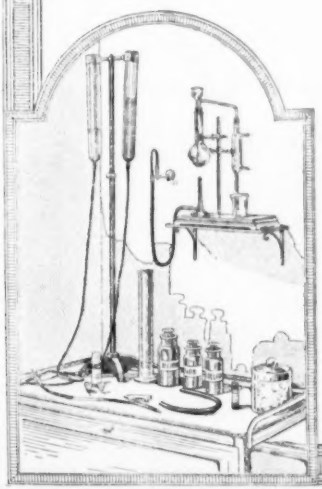

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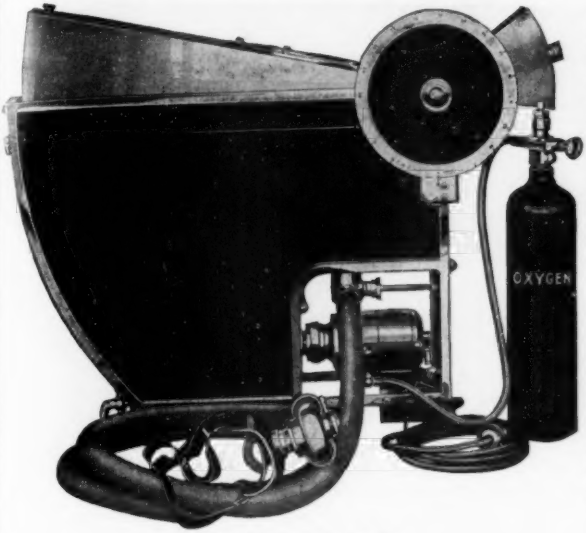

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